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(54) AROMATIC AMINE DERIVATIVES HAVING NOS INHIBITORY EFFECT

(57) Compounds represented by the general formula (1):

$$R_{1}$$
 N $(CH_{2})_{n}$ R_{3} $(CH_{2})_{m}$ X_{1} X_{2} X_{2} X_{3} X_{4} X_{5} X_{5}

(where R_1 and R_2 are typically a hydrogen atom; R_3 and R_4 are typically a hydrogen atom or a lower alkyl group; R_5 is typically a hydrogen atom; X_1 , X_2 , X_3 and X_4 are typically a hydrogen atom or a lower alkoxy group; A is typically an optionally substituted pyridine ring; m and n are each 0 or 1) have an NOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases and other pharmaceuticals.

Description

TECHNICAL FIELD

[0001] This invention relates to N-substituted aniline derivatives, more particularly to compounds represented by the general formula (I) that have a nitric oxide synthase (NOS) inhibiting action to suppress the production of nitric oxide (NO) and thereby prove effective against disorders and diseases in which excessive NO or NO metabolites are supposedly involved, namely, cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothromobotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus. The invention also relates to possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof. The invention further relates to preventives and therapeutics that contain said compounds, derivatives or pharmaceutically acceptable salts as active ingredients.

BACKGROUND ART

The number of deaths from cerebrovascular diseases in Japan had increased until 1970 when it began to decline mostly due to the improvement in their acute-phase therapy. Nevertheless, cerebrovascular diseases remain the second leading cause of death among adult diseases, next only to cancers. As for the incidence of cerebrovascular diseases, many statistical surveys indicate that it is generally constant and in view of the fact that the number of elderly persons will increase at an uncomparably faster speed in Japan than any other country in the world, the number of patients suffering from cerebrovascular diseases is estimated to increase rather than decrease in the future. The declining mortality and the growing population of aged people combine to increase the cases of cerebrovascular diseases in the chronic phase and this has presented with a national problem not only from the aspects of individual patients and society at large but also from the viewpoint of medical economics since patients with chronic cerebrovascular disease are inevitably involved in long-term care. In cerebral infarction that accounts for most cases of cerebrovascular diseases, cerebral arteries are occluded and blood deficit starting at the blocked site extends to the peripheral site, causing an ischemic state. The symptoms of cerebral infarction in the chronic phase are in almost all cases derived from the loss of neurons and it would be extremely difficult to develop medications or established therapeutic methods for achieving complete recovery from those symptoms. Therefore, it is no exaggeration that the improvement in the performance of treatments for cerebral infarction depends on how patients in an acute phase can be treated with a specific view to protecting neurons and how far their symptoms can be ameliorated in the acute phase. However, most of the medications currently in clinical use are antiplatelet drugs, anticoagulants and thrombolytics and none of these have a direct nerve protecting action (see Kazuo MINEMATSU et al., "MEDICINA", published by Igaku Shoin, 32, 1995 and Hidehiro MIZUSAWA et al., published by Nankodo, "Naika" 79, 1997). Therefore, it is desired to develop a drug that provides an effective therapy for cerebrovascular diseases, in particular cerebral infarction, by working in an entirely novel and different mechanism of action from the conventional medications.

[0003] A presently dominant theory based on genetic DNA analyses holds that NOS exists in at least three isoforms, namely, calcium-dependent nNOS (type 1) which is present constitutively in neurons, calcium-dependent eNOS (type 3) which is present constitutively in vascular endothelial cells, and apparently calcium-independent iNOS (type 2) which is induced and synthesized by stimulation with cytokines and/or lipopolysaccharides (LPS) in macrophages and many other cells (Nathan et al., FASEB J. 16, 3051-3064, 1992; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995). [0004] A mechanism that has been proposed as being most probable for explaining the brain tissue damage which accompanies cerebral ischemia is a pathway comprising the sequence of elevation in the extracellular glutamic acid level, hyperactivation of glutamic acid receptors on the post-synapses, elevation in the intracellular calcium level and activation of calcium-dependent enzymes (Siesjō, J. Cereb. Blood Flow Metab. 1, 155-185, 1981; Siesjō, J. Neurosurg. 60, 883-908, 1984; Choi, Trends Neurosci. 11, 465-469, 1988; Siesjō and Bengstsson, J. Cereb. Blood Flow Metab. 9, 127-140, 1989). As already mentioned, nNOS is calcium-dependent, so the inhibition of hyperactivation of this type of NOS isoforms would contribute to the neuro-protective effects of NOS inhibitors (Dawson et al., Annals Neurol. 32, 297-311, 1992).

[0005] As a matter of fact, the mRNA level of nNOS and the number of nNOS containing neurons start to increase early after focal cerebral ischemia in rats and their temporal alterations coincide with the development of infarction (Zhang et al., Brain Res. 654, 85-95, 1994). In addition, in a mouse model of focal cerebral ischemia, the percent inhibition of nNOS activity and the percent reduction of infarct volume correlate to each other at least in a dose range of N^G-nitro-L-arginine (L-NA) that produces a recognizable infarct volume reductive action (Carreau et al., Eur. J. Pharmacol. 256, 241-249, 1994). Further in addition, it has been reported that in nNOS knockout mice, the infarct volume

observed after focal cerebral ischemia is significantly smaller than that in the control (Huang et al., Science 265, 1883-1085, 1994).

[0006] Referring now to NO, it is at least one of the essences of endothelium-derived relaxing factor (EDRF) and, hence, is believed to take part in the adjustment of the tension of blood vessels and the blood flow (Moncade et al., Pharmacol. Rev. 43, 109-142, 1991). As a matter of fact, it was reported that when rats were administered high doses of L-NA, the cerebral blood flow was found to decrease in a dose-dependent manner as the blood pressure increased (Toru MATSUI et al., Jikken Igaku, 11, 55-60, 1993). The brain has a mechanism by which the cerebral blood flow is maintained at a constant level notwithstanding the variations of blood pressure over a specified range (which is commonly referred to as "autoregulation mechanism") ("NOSOTCHU JIKKEN HANDBOOK", complied by Keiji SANO, published by IPC, 247-249, 1990). The report of Matsui et al. suggests the failure of this "autoregulation mechanism" to operate. Therefore, if eNOS is particularly inhibited beyond a certain limit in an episode of brain ischemia, the cerebral blood flow will decrease and the blood pressure will increase, thereby aggravating the dynamics of microcirculation, possibly leading to an expansion of the ischemic lesion. It was also reported that in eNOS knockout mice, the infarct observed after focal cerebral ischemia was larger than that in the control but could be reduced significantly by administration of L-NA (Huang et al., J. Cereb. Blood Flow Metab. 16, 981-987, 1996). These reports show that eNOS-derived NO probably works protectively on the brain tissue through the intermediary of a vasodilating action, a platelet aggregation suppressing action and so forth.

[0007] The present inventors previously found that L-NA, already known to be a NOS inhibitor, possessed ameliorative effects on the brain edema and cerebral infarction following phenomena that developed after experimental cerebral ischemia (Nagafuji et al., Neurosci. Lett. 147, 159-162, 1992; Japanese Patent Public Disclosure No. 192080/1994), as well as necrotic neuronal cell death (Nagafuji et al., Eur. J. Pharmacol. Env. Tox. 248, 325-328, 1993). On the other hand, relatively high doses of NOS inhibitors have been reported to be entirely ineffective against ischemic brain damage and sometimes aggravating it (Idadecola et al., J. Cereb. Blood Flow Metab. 14, 175-192, 1994; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995). It should, however, be stressed that as a matter of fact, all papers that reported the changes of NO or NO-related metabolites in the brain and blood in permanent or temporary cerebral ischemic models agreed in their results to show the increase in the levels of those substances (Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0008] One of the reasons for explaining the fact that conflicting reports have been made about the effectiveness of NOS inhibitors in cerebral ischemic models would be the low selectivity of the employed NOS inhibitors for nNOS. As a matter of fact, no existing NOS inhibitors including L-NA and N^G-nitro-L-arginine methyl ester (L-NAME) have a highly selective inhibitory effect on a specific NOS isoform (Nagafuji et al. Neuroreport 6, 1541-1545, 1995; Nagafuji et al. Mol. Chem. Neuropathol. 26, 107-157, 1995). Therefore, it may well be concluded that desirable therapeutics of ischemic cerebrovascular diseases should have a selective inhibitory effect on nNOS (Nowicki et al., Eur. J. Pharmacol. 204, 339-340, 1991; Dawson et al., Proc. Natl. Acad. Sci. USA 88, 6368-6371, 1991; ladecola et al., J. Cereb. Blood Flow Metab. 15, 52-59, 1995; ladecola et al., J. Cereb. Blood Flow Metab. 15, 378-384, 1995; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

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[0009] It has also been suggested that nNOS inhibitors have the potential for use as therapeutics of traumatic brain injuries (Oury et al., J. Biol. Chem. 268, 15394-15398, 1993; MacKenzie et al., Neuroreport 6, 1789-1794, 1995; Mesenge et al., J. Neurotrauma. 13, 11-16, 1996; Wallis et al., Brain Res., 710, 169-177, 1996), headache and other pains (Moore et al., Br. J. Pharmacol. 102, 198-202, 1991; Olesen., Trends Pharmacol. 15, 149-153, 1994), Parkinson's disease (Youdim et al., Advances Neurol. 60, 259-266, 1993; Schulz et al., J. Neurochem. 64, 936-939, 1995; Hantraye et al., Nature Medicine 2, 1017-1021, 1996), Alzheimer's disease (Hu and El-FaKahany, Neuroreport 4, 760-762, 1993 Meda et al., Nature 374, 647-650, 1995), seizure (Rigaud-Monnet et al., J. Cereb. Blood Flow Metab. 14, 581-590, 1994), and morphine tolerance and dependence (Kolesnikov et al., Eur. J. Pharmacol. 221, 399-400, 1992; Cappendijk et al., Neurosci. Lett. 162, 97-100, 1993).

[0010] Upon stimulation by certain kinds of cytokines and/or LPS, iNOS is induced in immunocytes such as macrophages and glial cells and other cells, and the resulting large amount of NO will dilate blood vessels to cause a fatal drop in blood pressure. Therefore, it is speculated that an iNOS inhibitor may be effective against septic shocks (Kilbourn and Griffith, J. Natl. Cancer Inst. 84, 827-831, 1992; Cobb et al., Crit. Care Med. 21, 1261-1263, 1993; Lorente et al., Crit. Care Med. 21, 1287-1295, 1993). Further, it has been suggested that iNOS inhibitors are useful as therapeutics of chronic rheumatoid arthritis and osteoarthritis (Farrell et al., Ann, Rheum. Dis. 51, 1219-1222, 1992; Hauselmann et al., FEBS Lett. 352, 361-364, 1994; Islante et al., Br. J. Pharmacol. 110, 701-706, 1993), viral or nonviral infections (Zembvitz and Vane, Proc. Natl. Acad. Sci. USA 89, 2051-2055, 1992; Koprowski et al., Proc. Natl. Acad. Sci. USA 90, 3024-3027, 1993) and diabetes mellitus (Kolb et al., Life Sci. PL213-PL217, 1991).

[0011] The NOS inhibitors so far reported to have a certain degree of selectivity for nNOS are N^G-cyclopropyl-Larginine (L-CPA)(Lamberte et al., Eur. J. Pharmacol. 216, 131-134, 1992), L-NA (Furfine et al., Biochem. 32, 8512-8517, 1993), S-methyl-L-thiocitrulline (L-MIN) (Narayanan and Griffith, J. Med. Chem. 37, 885-887, 1994; Furfine et al.,

J. Biol. Chem. 37, 885-887, 1994; Furfine et al. J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995; Nagafuji et al., Neuroreport 6, 1541-1545, 1995), S-ethyl-L-thiocitrulline (L-EIN) (Furfine et al., J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995), and ARL 17477 (Gentile et al., WO95/05363; Zhang et al., J. Cereb. Blood Flow Metab., 16, 599-604, 1996).

[0012] In addition, the inhibitors that have been reported to have a certain degree of selectivity for iNOS are N^G-iminoethyl-L-ornithine (L-NIO) (McCall et al., Br. J. Pharmacol. 102, 234-238, 1991) and aminoguanidine (AG) (Griffith et al., Br. J. Pharmacol. 110, 963-968, 1993; Hasan et al. Eur. J. Pharmacol. 249, 101-106, 1993).

DISCLOSURE OF INVENTION

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[0013] An object of the present invention is to provide novel compounds that have an inhibitory effect on calcium-dependent nNOS which is present constitutively in the brain, particularly in neurons or an inducible and apparently calcium-independent iNOS and which are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, sub-arachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

[0014] As a result of the intensive studies made in order to attain the stated object, the present inventors found that aromatic amine derivatives represented by the general formula (I), or possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof have an inhibitory action on type 1 NOS and so forth, thereby exhibiting marked effectiveness as therapeutics of cerebrovascular diseases (especially as therapeutics of occlusive cerebrovascular diseases):

(where R₁ and R₂ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxycarbonyl group, or R₁ and R₂ may combine together to form a 3- to 8-membered ring;

 R_3 and R_4 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms; R_5 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;

 X_1 , X_2 , X_3 , and X_4 , which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, an optionally substituted lower alkyl group, a lower alkynyl group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=0)X_7$;

where X_5 and X_6 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring;

 X_7 is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX_8X_9 ;

where X_8 and X_9 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_8 and X_9 may combine together to form a 3- to 8-membered ring;

A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;

55 n and m are each an integer of 0 or 1).

[0015] The present invention has been accomplished on the basis of this finding.

[0016] The present invention also provides a process for producing a compound of the general formula (1) which is

represented by the reaction pathway (A):

Reaction pathway (A)

5 [0017]

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namely, a process in which a substituted aniline represented by the general formula (2) (where R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , X_4 , R_4 , R_5 is a hydrogen atom or an optionally substituted lower alkyl group) is reacted with a compound represented by the general formula (3) (where A has the same meaning as defined above; L is a leaving group) to produce a compound represented by the general formula (1).

[0018] The present invention further provides a process for producing a compound of the general formula (1) which is represented by the reaction pathway (B):

Reaction pathway (B)

[0019]

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namely, a process in which a substituted benzene represented by the general formula (9) (where R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , X_4 , X_5 , X_4 , X_5 , X_6 , X_8

BEST MODE FOR CARRYING OUT THE INVENTION

45 [0020] In the present invention, the 5- or 6-membered aromatic hetero ring as an example of A which contains at least one nitrogen atom as a hetero atom may be exemplified by a pyrrole ring, a pyrrole-1-oxide ring, a pyrazole-1-oxide ring, a pyrazole-1-oxide ring, an imidazole-1-oxide ring, an imidazole-1-oxide ring, an imidazole-1-oxide ring, an imidazole-1,3-dioxide ring, an isoxazole ring, an isoxazole-2-oxide ring, an oxazole-ring, an isothiazole-1,1-dioxide ring, an isothiazole-1,2-dioxide ring, an isothiazole-2-oxide ring, a thiazole-1-oxide ring, a thiazole-1,1-dioxide ring, a thiazole-3-oxide ring, a pyridine-N-oxide ring, a pyridazine-1-oxide ring, a pyridazine-1,2-dioxide ring, a pyrimidine ring, a pyrimidine-1-oxide ring, a

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the substituent in A is a hydroxyl group, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a lower alkoxy group, a lower alkyl group, a lower alkylthio group, $NX_{10}X_{11}$ or $C(=O)X_{12}$; where X_{10} and X_{11} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_{10} and X_{11} may combine

together to form a 3- to 8-membered ring;

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 X_{12} is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkyl group or $NX_{12}X_{14}$;

- where X_{13} and X_{14} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_{13} and X_{14} may combine together to form a 3- to 8-membered ring;
- the lower alkyl group is a straight-chained alkyl group having 1 6 carbon atoms, or a branched or cyclic alkyl group having 3 8 carbon atoms and may be exemplified by a methyl group, an ethyl group, an n-propyl group, an n-butyl group, an n-pentyl group, an n-hexyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an i-pentyl group, a neopentyl group, a t-pentyl group, a ni-hexyl group, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or the like:
- the lower alkenyl group is a straight-chained alkenyl group having 2 6 carbon atoms or a branched alkenyl group having 3 6 carbon atoms and may be exemplified by a vinyl group, an allyl group, a 1-butenyl group, a 1-pentenyl group, a 2-butenyl group, a 2-butenyl group, a 2-butenyl group, a 2-butenyl group or a 1-methyl-1-propenyl group or the like;
- the lower alkynyl group is a straight-chained alkynyl group having 2 6 carbon atoms or a branched alkynyl group having 3 6 carbon atoms and may be exemplified by an ethynyl group, a 1-propynyl group, a 1-butynyl group, a 2-propynyl group, a 2-butynyl group, a 2-pentynyl group, a 2-hexynyl group, a 1-methyl-2-propynyl group, a 3-methyl-1-butynyl group or a 1-ethyl-2-propynyl group or the like;
 - the lower alkoxy group is a straight-chained alkoxy group having 1 6 carbon atoms or a branched or cyclic alkoxy group having 3 8 carbon atoms and may be exemplified by a methoxy group, an ethoxy group, an n-propoxy group, an n-butoxy group, an n-pentoxy group, an n-hexoxy group, an i-propoxy group, an i-butoxy group, a sec-butoxy group, a t-butoxy group, an i-pentoxy group, a neopentoxy group, a t-pentoxy group, an i-hexoxy group, a cycloperopoxy group, a cyclobutoxy group, a cyclopentoxy group, a cyclohexoxy group, a cycloheptoxy group or a cyclooctoxy group or the like;
- the lower alkylthio group is a straight-chained alkylthio group having 1 6 carbon atoms or a branched or cyclic alkylthio group having 3 8 carbon atoms and may be exemplified by a methylthio group, an ethylthio group, an n-propylthio group, an n-butylthio group, an n-hexylthio group, an i-propylthio group, an i-pentylthio group, an i-pentylthio group, a neopentylthio group, a t-pentylthio group, a cyclopentylthio group, a cyclopentylthio
 - the acyl group is not only a formyl group but also an alkylcarbonyl group the alkyl portion of which is a lower alkyl group, as well as an arylcarbonyl group and may be exemplified by an acetyl group, a propionyl group, a butyryl group, a valeryl group, an isobutyryl group, an isobutyryl group, an isobutyryl group, a pivaloyl group, a benzoyl group, a phthaloyl group or a toluoyl group or the like:
- the lower alkoxycarbonyl group is an alkoxycarbonyl group the alkyl portion of which is a lower alkyl group and may be exemplified by a methoxycarbonyl group, an ethoxycarbonyl group, an n-propoxycarbonyl group, an n-butoxycarbonyl group, an n-pentoxycarbonyl group, an i-propoxycarbonyl group, an i-butoxycarbonyl group, a sec-butoxycarbonyl group, a t-butoxycarbonyl group, an i-pentoxycarbonyl group, a neopentoxycarbonyl group, a t-pentoxycarbonyl group, an i-hexoxycarbonyl group, a cyclopropoxycarbonyl group, a cyclobutoxycarbonyl group, a cyclopentoxycarbonyl group, a cyclohexoxycarbonyl group, a cyclohexoxycarbonyl group, a cyclohexoxycarbonyl group, or a cyclooctoxycarbonyl group or the like;
 - the halogen atom is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom;
 - the leaving group is a halogen atom, a trifluoromethanesulfonyloxy group, a p-toluenesulfonyloxy group or a methanesulfonyloxy group;
- the substituent in the case where R₁, R₂, R₃, R₄, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, or X₁₄ is an optionally substituted lower alkyl group, an optionally substituted lower alkylthio group or an optionally substituted lower alkoxycarbonyl group may be exemplified by a halogen atom, a phenyl group optionally substituted by a halogen atom or a lower alkyl group or a cyclic alkyl group having 3 8 carbon atoms;
- the ring as the 3- to 8-membered ring optionally formed by R₁ and R₂ taken together, the ring as the 3- to 8-membered ring optionally formed by X₅ and X₆ taken together, the ring as the 3- to 8-membered ring optionally formed by X₈ and X₉ taken together, the ring as the 3- to 8-membered ring optionally formed by X₁₀ and X₁₁ taken together, and the ring as the 3- to 8-membered ring optionally formed by X₁₃ and X₁₄ taken together are each a hetero ring containing at least one nitrogen atom as a hetero atom and may be exemplified by a pyrrole ring, a pyrazole ring, an imidazole ring, a triazole ring, an azeridine ring, an azeridine ring, a pyrrolidine ring, a piperidine ring, a piperazine ring, a morpholine ring, a thiomorpholine ring, an azepane ring or an azocane ring or the like;
 - the ring as the monocyclic or fused ring having 3 10 carbon atoms that is optionally formed by R_3 and R_4 taken together may be exemplified by a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclopentane ring,

a cycloheptane ring, a cyclooctane ring, an indane ring or a tetralin ring or the like;

 NX_5X_6 , NX_8X_9 , $NX_{10}X_{11}$, and $NX_{13}X_{14}$ may be exemplified by an amino group, a methylamino group, a benzylamino group, an ethylamino group, a dimethylamino group, an ethylamino group, a piperidine-1-yl group, a morpholine-4-yl group, an acetamido group, a benzamido group, an N-methylacetamide group, a benzamido group, a tert-butoxycarbonylamino group, an N-methyl-t-butoxycarbonyl-amino group, a pyrrole-1-yl group, a pyrazole-1-yl group, an imidazole-1-yl group, a triazole-1-yl group, an azetidine-1-yl group, a pyrrolidine-1-yl group, a piperidine-1-yl group, a pyrrolidine-4-yl group, a piperidine-1-yl group, a morpholine-4-yl group or a thiomorpholine-4-yl group or the like;

C(=O)X₇ may be exemplified by a formyl group, a carboxyl group, an acetyl group, a propionyl group, a cyclobutyryl group, a methoxycarbonyl group, an ethoxycarbonyl group, a t-butoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, an N-ethylcarbamoyl group, an N-ethylcarbamoyl group, an N-ethylcarbamoyl group, a pyrrolidinecarbonyl group, a piperidinecarbonyl group or a morpholinecarbonyl group or the like; R₁ and R₂ are preferably a hydrogen atom;

 R_3 and R_4 are preferably a hydrogen atom, a lower alkyl group having 1 - 3 carbon atoms or a monocyclic ring having 3 - 5 carbon atoms, with a hydrogen atom, a methyl group, an ethyl group or a cyclobutyl group being particularly preferred;

R₅ is preferably a hydrogen atom;

X₁, X₂, X₃, and X₄ are preferably a hydrogen atom, a halogen atom, a lower alkyl group having 1 - 3 carbon atoms or a lower alkoxy group having 1 - 3 carbon atoms, with a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group or pyridine ring, and more preferred is a bearene or pyridine ring.

A is preferably an optionally substituted benzene or pyridine ring, and more preferred is a benzene or pyridine ring that is substituted by a nitro group, a lower alkyl group having 1 - 3 carbon atoms, a lower alkoxy group having 1 - 3 carbon atoms or a lower alkylthio group having 1 - 3 carbon atoms, with a 6-methoxy-3-nitrobenzene-2-yl group, a 6-methyl-3-nitropyridine-2-yl group, a 6-methoxy-3-nitro-pyridine-2-yl group or a 4-methylpyridine-2-yl group being particularly preferred;

m and n are such that if they are both zero, the substituents other than X_1 , X_2 , X_3 , and X_4 are preferably meta-substituted on the benzene nucleus whereas if m + n = 1, the substituents other than X_1 , X_2 , X_3 , and X_4 are preferably ortho- or para-substituted on the benzene nucleus.

[0021] Preferred compounds represented by the general formula (1) are 2-(3-aminomethylphenylamino)-6-methoxy-30 3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-3-ethyl-3nitropyridine, 2-(3-aminomethylphenylamino)-6-ethoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitrobenzene, 2-(3-aminomethylphenylamino)-6-methoxy-3nitrobenzene, 2-(3-aminomethyl-2-methylphenylamino)-6-methoxy-3-nitropyridine, 2-(4-aminoethylphenylamino)-6methoxy-3-nitropyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2methoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-fluorophenylamino)-6-methoxy-3-nitro-pyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-6-methoxy-3-nitropyridine. 2-(3-aminomethyl-2-chlorophenylamino)-6-methoxy-3-nitropyridine. 2-(3-aminomethylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-2methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4ethoxyphenylamino)-4-methylpyridine, 2-(2-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-chlorophenylamino)-4-methylpyridine, 2-(3-(1-amino-cyclobutyl)phenylamino)-4-methylpyridine, 2-(4-aminoethylphenylamino)-4methylpyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chlorophenylamino)-4methylpyridine, 2-(3-aminomethyl-2-(n-propoxy)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chloro-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylaminomethylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylaminomethylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylaminomethylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylaminomethylpyridine, 2-(3-aminomethylphenylaminomethylp thyl-2-methoxyphenylamino)-4-methylpyridine and 2-(3-aminomethyl-2-(i-propoxy)phenylamino)-4-methylpyridine.

[0022] In addition to the compounds represented by the general formula (1), the present invention also encompasses their possible tautomers, stereoisomers, optionally active forms and mixtures thereof.

[0023] The compounds of the invention which are represented by the general formula (1) may typically be synthesized by the following schemes:

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[0024] The compound represented by the general formula (1) can be synthesized by reacting a compound of the general formula (2), used as a starting material, with a compound of the general formula (3).

[0025] In the general formulas (1), (2) and (3), R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, A, L, n and m

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(8)

each have the same meanings as defined above.

[0026] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (2) with the compound of the general formula (3) in the presence of a base such as potassium carbonate, triethylamine, diisopropylethylamine, potassium t-butoxide or sodium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphophinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or 1,4-dioxane, at a temperature between room temperature and the boiling point of the reaction mixture. Preferably synthesis can be made by performing the reaction in the presence of triethylamine or diisopropylethylamine in dimethylformamide at 60°C or by performing the reaction in the presence of potassium carbonate, potassium t-butoxide or sodium t-butoxide, with a palladium catalyst and a ligand diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl added, in acetonitrile or toluene at a temperature between 80°C and the boiling point of the reaction mixture.

[0027] The compound represented by the general formula (1) can also be synthesized by reacting a compound of the general formula (9), used as a starting material, with a compound of the general formula (10).

[0028] In the general formulas (1), (9) and (10), R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , X_4 , R_5 , A, L, m and n each have the same meanings as defined above.

[0029] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (9) with the compound of the general formula (10) in the presence of a base such as potassium carbonate, triethylamine, potassium t-butoxide or sodium t-butoxide, preferably in the presence of potassium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphosphinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, preferably a palladium catalyst and a ligand diphenylphosphinoferrocene being added, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or dioxane, preferably in toluene, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at 80°C.

[0030] Among the compounds represented by the general formula (1), one which is represented by the general formula (5) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$ can also be synthesized starting with a compound of the general formula (4) with the leaving group attached.

[0031] In the general formulas (4), (5), (12), (13) and (14),

R₁, R₂, R₃, R₄, X₁, X₂, X₃, X₄, L, m and n each has the same meanings as defined above;

R₆ is an electron withdrawing group such as a nitro group, a cyano group, a trifluoromethyl group or C(=O)X₇;

 R_7 and R_8 are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a hydroxyl group, a lower alkyl group, a lower alkylthio group, NX_5X_6 or $C(=O)X_7$;

where X_5 , X_6 , and X_7 each has the same meanings as defined above;

 R_{11} is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$;

R₁₂ and X₁₀ are each a lower alkyl group;

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X₁₁ is a hydrogen atom or a lower alkyl group.

[0032] Stated more specifically, the compound represented by the general formula (5) can also be synthesized from the compound of the formula (4) by desirably reacting it with a corresponding compound of the general formula (12), (13) or (14) in the presence of a base such as triethylamine or sodium hydride in a solvent inert to the reaction such as dimethylformamide, tetrahydrofuran or acetonitrile at a temperature between room temperature and the boiling point of the reaction mixture.

[0033] Among the compounds represented by the general formula (1), one which is represented by the general formula (11) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkyl group can also be synthesized by decarboxylation a compound obtained by performing a nucleophilic substitution on a lower alkyl dicarbonate corresponding to a compound of the general formula (4) with the leaving group attached.

[0034] In the general formulas (4) and (11),

 R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , X_1 , X_2 , X_3 , X_4 , m and n each have the same meanings as defined above; and R_{14} is a lower alkyl group.

[0035] Stated more specifically, the compound represented by the general formula (11) can also be synthesized from the compound of the general formula (4) by desirably reacting it with a corresponding lower alkyl dicarbonate in the presence of a base such as sodium hydride in a solvent inert to the reaction as exemplified by dimethylformamide, tetra-

hydrofuran or acetonitrile, preferably in dimethylformamide, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature and thereafter subjecting the product to reaction in aqueous sulfuric acid at the boiling point of the reaction mixture.

[0036] Examples of the lower alkyl dicarbonate include dimethyl malonate, diethyl malonate, diethyl methylmalonate, diethyl n-propylmalonate, diethyl n-butylmalonate, diethyl i-butylmalonate, diethyl n-pentylmalonate and so forth.

[0037] Among the compounds represented by the general formula (1), one which is represented by the general formula (7) where A is an optionally substituted pyridine ring and one of the substituents present is an amino group can also be synthesized by reducing the nitro group in the corresponding general formula (6).

10 [0038] In the general formulas (6) and (7),

R₁, R₂, R₃, R₄, m and n each have the same meanings as defined above;

 R_6 , R_7 , and R_8 are each a hydrogen atom, a halogen atom, a trifluoromethyl group, a hydroxyl group, a lower alkylthio group, $R_8 = R_8 + R_$

where X_5 , X_6 , and X_7 each have the same meanings as defined above;

 X_1 , X_2 , X_3 , and X_4 are each a hydrogen atom, a halogen atom, a phenyl group optionally substituted with a halogen atom and/or a lower alkyl group, a hydroxyl group, an optionally substituted lower alkyl group, X_5 or X_5 ;

where X₅, X₆, and X₇, each have the same meanings as defined above.

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[0039] Stated more specifically, the compound represented by the general formula (7) can also be synthesized by subjecting the compound of the general formula (6) to catalytic reduction in a solvent inert to the reaction as exemplified by ethanol, methanol, ethyl acetate, acetic acid or 1,4-dioxane, preferably in ethanol or methanol, in a hydrogen atmosphere at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature, with palladium-carbon, Raney nickel or platinum oxide used as a catalyst, or by performing reduction using nickel (II) chloride or sodium borohydride, so as to reduce the nitro group.

[0040] Among the compounds represented by the general formula (1), one which is represented by the general formula (8) where A is an optionally substituted pyridine ring and one of the substituents present is NR_9R_{10} can also be synthesized with a compound of the general formula (7) used as a starting material.

30 [0041] In the general formulas (7), (8), (15), (16) and (17),

 R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_{12} , X_1 , X_2 , X_3 , X_4 , L, m and n each have the same meanings as defined above; R_9 is a hydrogen atom or a lower alkyl group;

R₁₀ is a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;

R₁₃ is a lower alkyl group optionally substituted by a phenyl group; and

X is a halogen atom.

[0042] Stated more specifically, the compound represented by the general formula (8) can also be synthesized from the compound of the general formula (7) by desirably reacting it with a corresponding compound of the general formula (15), (16) or (17) in the presence of a base such as triethylamine or potassium carbonate in a solvent inert to the reaction at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature.

[0043] If in the process of synthesizing the compounds represented by the above formulas (1), (5), (7), (8) and (11), a protective group is necessary for the primary or secondary amino group, they are first protected either with a suitable resin or with one of the appropriate protective groups described in Green and Wuts, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS", 2nd Edition, John Wiley & Sons Inc., p. 309, 1991, and thereafter the respective reactions are performed. If necessary, the protected groups may be subjected to a deprotecting reaction. Examples of the amino protecting group include a t-butoxycarbonyl group, a trifluoroacetyl group and so forth.

[0044] The amino protecting reaction such as t-butoxycarbonylation may be performed by reacting the respective compound with di-t-butyl dicarbonate in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or methylene dichloride, dimethyl-formamide or 1,4-dioxane in the presence of an organic base such as triethylamine or 4-dimethylamiopyridine at a temperature between 0°C and room temperature.

[0045] The amino protecting reaction may also be performed with a Wang resin by reacting the respective compound with a 4-nitrophenyloxycarbonyl-Wang resin (Tetrahedron Lett., 37, 937-940 (1996)) in a solvent inert to the reaction as exemplified by methylene chloride, dimethylformamide or 1,4-dioxane in the presence of an organic base such as 4-methylmorpholine, triethylamine or 4-dimethylaminopyridine at a temperature between 0°C and room temperature.

[0046] If the protecting group is a t-butoxycarbonyl group or the Wang resin mentioned above, a reaction for deprotecting the amino group is preferably performed in a solvent inert to the reaction as exemplified by methanol, ethanol,

1,4-dioxane or methylene chloride or without using any solvent at all, with the aid of a deprotecting agent such as trifluoroacetic acid, hydrochloric acid, sulfuric acid or methanesulfonic acid at a temperature between 0°C and room temperature, with the use of anhydrous conditions, room temperature and trifluoroacetic acid being particularly preferred.

[0047] If the compounds of the invention which are represented by the general formula (1) have asymmetric carbons in their structure, the pure forms of their stereoisomers and optically active forms can be obtained by known techniques in the art, such as chromatography on optical isomer separating columns and fractional crystallization.

[0048] Pharmaceutically acceptable salts of the compounds of the invention which are represented by the general formula (1) may be of any types as long as they are pharmaceutically acceptable salts and typical examples include salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobrobromic acid and hydroiodic acid, salts with organic acids such as formic acid, acetic acid, oxalic acid and tartaric acid, salts with alkali metals such as sodium and potassium, and salts with alkaline earth metals such as calcium and magnesium.

[0049] The compounds of the invention or salts thereof may be formulated with suitable excipients, adjuvants, lubricants, antiseptics, disintegrators, buffering agents, binders, stabilizers, wetting agents, emulsifiers, coloring agents, flavoring agents, fragrances, etc. to form tablets, granules, subtilized granules, powders, capsules, syrups, elixirs, suspensions, emulsions, injections, etc. for oral or parenteral administration. When the cerebrovascular diseases to be treated are in a hyperacute phase (immediately after the stroke), an acute phase (from the stroke to 2 or 3 days later) or in a subacute phase (2 or 3 days up to 2 weeks after the stroke), administration is effected primarily by intramuscular or intravenous injection. In addition, oral administration may be performed in a chronic phase (the third week after stroke and onward) if the patient admits ingestion.

[0050] The compounds of the invention or salts thereof may be administered in doses that vary with the physical constitution of the patient, his or her age, physical condition, the severity of the disease, the time of lapse after the onset of the disease and other factors; typical daily doses range from 0.5 to 5 mg/body for oral administration and from 1 to 10 mg/body for parenteral administration. It should generally be noted that even if the same dose is administered, the plasma concentration may sometimes vary considerably between patients; hence, an optimal dose of the drug should ideally be determined for each patient on the basis of a monitored plasma concentration of the drug.

[0051] If the compounds of the invention or salts thereof are to be formulated as preparations for internal application, lactose, sucrose, sorbitol, mannitol, starches such as potato starch or corn starch, starch derivatives and common additives such as cellulose derivatives or gelatin are suitably used as vehicles, with lubricants such as magnesium stearate, carbowaxes and polyethylene glycol being optionally added concurrently; the resulting mixtures may be formulated in the usual manner into granules, tablets, capsules or other forms suitable for internal application.

[0052] If the compounds of the invention or salts thereof are to be formulated as aqueous preparations, effective amounts of the principal ingredients may be dissolved in distilled water for injection, with antioxidants, stabilizers, dissolution aids, buffering agents, preservatives, etc. added as required and, after complete solutions are formed, they are filtered, filled into ampules and sealed in the usual manner and sterilized by a suitable medium such as high-pressure vapor or dry heat so as to prepare injections.

[0053] If the compounds of the invention or salts thereof are to be formulated as lyophilized preparations, aqueous solutions having the principal ingredients dissolved in distilled water for injection may be freeze-dried in the usual manner; depending on the need, excipients that provide for easy lyophilization, such as sugars (e.g. lactose, maltose and sucrose), sugar alcohols (e.g. mannitol and inositol), glycine and the like, may be added before freeze-drying is performed in the usual manner to make the intended preparations.

Examples

[0054] Lists of the compounds prepared in the Examples of the invention are given in Tables 1 - 37 below.

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			_	_	_	_	_	_	_					:	÷			, ' -	
			salt		Ę		ЮН		НСІ		ЮH		2HCI		2HCF		НСІ	HCI.	: !
5			Яŝ	I	I	н	I	I	H	I	н	Ή	н	I	I	I	Н	Ξ	
			Ε	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		S S	2	I	Ξ	Ι	I	Ι	I	I	Ξ.	I	I	I	I	н	I	I	
10		E E	3	Ξ	Ξ	I	I	I	I	I	I	Ξ	H	Ξ	I	I	I	Ŧ	छं
		4	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	employed
15		£ 2 2 8 0	22	CO ₂ tBu	Ξ	CO ₂ tBu	I	იფშით	Ξ.	I	I	იფშიე	I	CO ₂ tBu	I	CO ₂ lBu	Ŧ	Ŧ	
		4 C	Æ	ကရႊဝ၁	I	пв _і гоэ	I	മുഗോ	π	၈ရးငီတ	I	ng ₁ ZOO	H	CO2lBu	I	CO2 ^{tBu}	I	I	(2)-(1)
20		# 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Substitution position of Pe	3	3	3	3	3	3	3	3	9	3	3	3	. 6	3	3	structural formulas of benzene ring.
		₹ 6	X4.2	F.H	Р.	н-9	Н-9	н-9	H-9	H-9	F-H	H-9	6-н	н-9	Н-9	н-9	H-9	н-9	l for ing.
25	က	3 2 3	X3.2	F.	5-Н	5-H	5.H	9-H	5-H	F.	5-H	H.S	5-н	9-H	9-Н	5.H	5.H	5-H	structural fo benzene ring.
		£ % %	x2.5	Ŧ	H-+	H-4	Ŧ	H-4	4-H	Ŧ	Ĩ	Ŧ	+ +	4-H	H+	H-4	H.4	4 . H	struc
30	Table	2 - 8	x1.5	H-2	2-H	2·H	2-H	2-H	2-H	2-H	2·H	2-H	2•H	2-H	2-H	2-H	2.H	2-H	the
		3-C	Rg.1	6-NHEt	6-NHE	8-NHmPr	8-NHnPr	6-NMe2	6-NMe ₂	ე დ	ភ្	6-OM6	6-OMe	Н-9	당	6-OMe	6-OMe	6-OMe	positions in positions on
35		8 8 8 8	R8.1	F.	F.F.	H.S	H-6	5-H	F.S	H-S	5.H	9-H	5-H	H-S	9•H	9-H	S.H	5-H	ositi ositi
		2 - 3	R7.1	Ŧ	Ŧ	₹	Ŧ	H.4	±	1	H.	Ŧ	Ŧ.	H-4	Ŧ.	±	4.H	1.4 H	
40		×	Substitution position of A	2	2	2	2	2	2	2	8	2	2	2	2	2	2	2	substitution substitution R1 R2
		~ (D -/ *	89	NO ₂	ZON NO.	ZON	20N	2 0≥	20 ₂	н2оэ	СО2Н	I	I	CF3	CF3	СО2Мв	СО2Ме	CO2H	1 1
45		CH ₂)m	2	z	z	z	z	z	z	z	z	z	z	z	z	z	z	z	Press Press C-C
		F	>	CR ₆	CR6	CR6	CR6	CR6	CRe	ည မွ	CR ₈	C.R.	CRe	CR6	CR ₆	CR ₆	CR6	CR ₆	s re
50		-(C V 2)	4	(2)	(2)	(2)	(3)	8	(3)	2	8	(2)	<u>(S</u>	(2)	(2)	8	(2)	8	neral neral
		R3 X-1 X-1 CH2N-C-1 CH2) m 1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X	7. 7.	31	32	33	34	35	36	37	38	38	40	ţ	42	43	7	45	*1:Numerals represent *2:Numerals represent R3 *:W = -(CH2)m-C-(CH2)n-R4

															•	• • •	٠.		•			
			salt	할	2HCI	귳	호	2HC	2HCI	호	Σ̈	Ξ̈	Ē	ΞΉ	HC	HC	Ξ	HC				
•			Rs	Ξ	Ŧ	Ξ	I	Ξ	Ξ	I	I	Ξ	I	I	I	I	Ξ	I				
5			E	0	0	0	0	0	•	0	•	0	0	0	0	0	0	0	İ			
		88	2	Ξ	I	I	Ξ	Ī	I	I	Ŧ	Ξ	I	I	I	Ŧ	I	I				
		~ * de 5	3	Ŧ	Ξ	I	I	I	I	I	I	Ξ	I	I	I	I	÷	I				
10		E - E	c	0	0	0	•	0	0	0	0	0	0	•	0	•	•	0	÷			
15		4 / 2 E 8	R ₂	Ξ	Ξ	I	I	I	I	Ξ	I	I	H	I	Ξ	I	I	СН2СН2СІ	(2)-(7) employed			
15		, , , , , , , , , , , , , , , , , , ,	Æ	Ac.	Ξ	Bz	I	I	I	r	I	Bn	н	I	I	СН2СН2Рћ	Ξ	CH2CH2CI				
20		F 2 8 8	Subst	6	က	6	9	3	3	e	3	3	3	3	3	3	ဗ	3	formulas of			
		88 6	×4.5	F.	H-9	6-H	H-9	F.	н-9	F.H	Н-9	6-н	н-9	н-9	F-H	Н-9	H-9	н-9	for			
25	4	3 3 - 3	x3.5	ూ	팏	S-H	9-H	5-н	S-H	5-H	5.H	5-H	5-H	S-H	F-5	5-H	5-H	9-Н	ura]			
30	Table	6 49 A 2 47	x2.5	Ŧ	H-4	4-c, clobutyl	4-cyclopentyl	4-piperidino	4-O(CH2)2Ph	4-H	4-H	4-H	4-H	4-H	4·H	4-H	4-H	4-H	the structural for			
		- E	x1.5	2·H	2-H	2-H	2-H	2-H	2-H	2-H	2-H	2-Н	2-H	2-H	2-H	2-н	2-H	H-2	라 E			
		R ₉ A 2 2 4	F.g.	H-0	Ŧ.	H-9	н-9	¥-9	Н-9	6-148	6-Et	Jdu-9	6-ipr	장	6-0Et	6-OnPr	êOP.	HS-9	positions positions			
35		(S)	E	Ŧ.S	S.H	F.S	5.H	5.H	5-H	S.H	퍇	5-H	5.H	5.H	5.H	5-H	F.F	5-H				
		# #	R7.1	4-OBn	4-0Bn	H-4	¥÷	4.H	Ŧ	4.H	4 H-4	4-H	4-H	4. H-4	H-4	4. H-	1 +	4.H	ution			
40		× 2 - × 4 -	Substitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	8	2	substitution substitution		<u>۔</u>	عمر
		׏ʯ×	æ	I	H	I	н	I	I	20N	40 2	NO ₂	20N	NO2	Š Š	Š	Ş 02	NO ₂	sent		CH2)n-	ì
45		(CH ₂)	7.	Z	z	Z	z	z	z	z	z	z	z	z	z	z	z	z	pre	. æ.	۲ ۷-	- à
		g-0-g	٨	CR6	CR ₆	CR6	CR6	CRe	CR6	CR6	CR6	CR6	СВв	CR6	CR6	CR6	CR6	(2) CR ₆	S re		±2,∓	ì
		(CH ₂)	4	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	eral		\$	
50		R3 X1 X2 R4 X X (CH2)n-C-(CH2)m4 X X X4 X5 X4 X1 X3 X4 X1 (1)	Er. No.	46	47	48	49	20	51	52	53	54	55	99	57	58	59	09	*1:Numerals represent *2:Numerals represent		. W = -(CH ₂)m-C-(CH ₂)n-	K

			/\ I	π I	7 L	π	7 I	7 I	π	\overline{a}	スト	5 L	ನ I	5 I	ပ္ ၂	υl	ပ္က				
		sal	홋	포	모		皇	포	도	단	를 무		ᆉ	ğ	2HCI	2HCI	2HCI				
5	60	RS	Ξ	Ŧ	ŝ	ឃ	Ξ	Ξ	I	I	ubı	8	튭	=	=	=	エ				
	A TON	ε	•	•	•	0	•	•	٥	0	0	<u> </u>	•	0	0	0	의				
	£	ž	I	Ξ	ェ	ᄑ	Ξ	Ξ	I	I	Ξ	Ξ	ᄑ	Ŧ	Ŧ	Ξ	Ξ	Ġ.			
10	¥.	F.	I	I	I	I	I	Ξ	H	н	I	Ξ	Ξ	=	Ξ	I	Ξ	employed			
	7 x 8	٥	0	0	0	0	٥	0	0	0	0	0	0	0	0	•	•				
15	£&@	R ₂	Ξ	Ŧ	I	I	I	H	Ξ	I	Ξ	Ξ	I	I	I	ェ	I	- (7)			
	A 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	R ₁	Ŧ	Ξ	I	Ξ	I	I	H	I	Ξ	Ξ	Ξ	Ξ	I	Ξ	I	(2)			
20	8 5 5 8 6	Substitution position of Pe	3	3	3	3	က	3	၉	က	3	9	၉	9	3	9	9	formulas of ng.			
	A 2. 3	x4.5	н-9	H-9	н-9	H-9	н-9	н-9	H-9	H-9	P-9	Н-9	6-н	H-0	H-9	6-H	H-9	for ng.			
25	**************************************	x3.2	5-H	5-H	5.H	5-H	5-H	5-H	5-NHAC	H.S.	F.S	5-NO2	5-H	5.H	5-H	Ş-B	5-H	structural fo			
16 5	A	x ₂ .5	¥.	F-4	1.4 T	4-H	H-4	H-4	±.4	4-NHBn	4-NO ₂	H-4	4-H	4·H	4-F	4·H	4-CH2Br				
e Table	8 2 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	x1.2	2-H	2-H	2·H	2·H	2-H	2·H	7.H.2	2-H	1.2 H.2	2-H	2.Н	2·H	2-H	2·H	5-Н	the the			
	2×4 2×5 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	R ₉ ·1	6-SMe	6-SEI	9-Supr	6-SiPr	6-OMe	6-Et	6-OMe	SEI.	6-OM8	g.	6-OMe	6-EI	6-OM8	6-Et	6-OMe	ons in			
35	6 5 6 8 8 8	r. E	5-H	F.F.	5-H	5.H	9-H	5.H	5-NO ₂	5-NO2	H-S	H.S	5-H	5.H	9-H	5-H	H.S.	positions positions			
	2 - 3	R7.1	± 4	H.4	± 4	H.	4-NO ₂	4-NO ₂	H-4	H-4	Ŧ.	H-4	H.4	H.4	H-4	#. 1	±4	ion g uoi			
40	8	tution on of A	2	2	2	2	2	2	8	2	2	2	2	2	2	2	2	substitution substitution	.	. ر	A2
	******* %**- <u>*</u> **	29		Š	Ş	Ş	I	Ξ	Ξ	Ξ	H202	H200	CO2Me	СО2Ме	CONH2	CONH ₂	CF3			Y	
45	£2,	7	z	z	z	z	z	z	z	z	z	z	z	z	z	z	z	pre	۔ چ-	<u>ဗို</u>	-œ*
	8-0-4 0 €	>	CR ₆	S. B.	မ္မ	S, B,	S. B.	S B	ဗ္ဗ	85	S, S	CRe	CR ₆	CH ₆	CRe	CRe	C _B e	S Y S		±2)ш−	
	CH2bn	 	8	8	8	2	8	8	8	+	+-	8	8	8	8	(2)	8	eral		<u>,</u>	
50	R2 X1 X2 R2 V-(CH2)n-c-(CH2)m-t-(CH2)m	Ex. No.	61	62	63	64	65	99	29	89	69	70	7.	72	22	74	75	*1:Numerals		w = -(CH2)m-¢-(CH2)n	

			salt	2HCI	H C	HC	2HCI	2HCI	2HCI	2HCI	HC	Ę	HCI	HCI	호	Ę	HCI	Ö				
			R _S	H	н	H	н	Н.	H	Н	I	I	н	Н	I	I	н	Ŧ				
5			E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
10		E	æ	Ι	н	H	н	H	н	н	н	н	I	сн2сн2он	I	I	Ι	I				
		5 A= 26	R ₃	н	н	н	I	н	I	H	I	I	н	сн2сн2он	I	I	H	I	employed			
15		2-29	c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3			
	•	8	P2	Ξ	H	Н	H	I	H	Ŧ	н	I	н	н	I	I	Ξ	H	(2) - (7)			
			R	Ξ	H	Ξ	I	I	I	I	I	Ξ	H	H	I	I	I	Ŧ	of (
20			Substitution position of We	3	3	3	ε	3	ε	9	£	£	ε	ε	ε	ε	ε	ε	structural formulas o benzene ring.			
		4	X4.5	6-H	6-H	6-Н	6-H	6-Н	H-8	P-H	F	H-8	6-н	8-H	9-H	B-H	6-H	H-9	for the			
25		254	x3.5	SH	9-Н	5-H	5-H	F-H	Ŧ	P.H	H	Ь-6	5-MB	5-Et	S-H	9-H	5-H	5-H	ura]			
30	Table 6	H, H	x2.5		4-Me	4.npr	4-NHMe	4-NHEI	4-NMe2	4-pyrrolidin-1-yl	40H	4-0Ei	F-4	H-4	H-4	H-4	H-4	H-4	the			
		w _0	x1,5	2-H	2-H	5-н	2-H	7-H-	2-H	7. F.	Ŧ.	2.H	2-H	2.F	2	2-Me	20H	2-OMe	ns in			
<i>35</i>		/8 5	%	6-Et	8-OMe	H-0	H-9	F.	H-9	F.	H-0	H.	H.	H.9	F.H	H-9	F.	H-9	ositic			
		1 - 8 m - 8	. B.	Ŧ	F.	S.H.	F.	1-6 H-6	S-H	F.	S.	F.	F.	Ŧ.	F.	F.	5.H	S.H	ë ë V			
		4 A A	R7.1	¥.	H-4	H.	4-H	4-H	H-4	H-4	H.4	4 H	H-4	4-H	4 H	4.H	4-H	H-4	tutio			
40		× × × × × × × × × × × × × × × × × × ×	Substitution position of A	2	2	2	2	2	2	2	2	7	2	2		7	2	2	substitution positions substitution positions	ار کا	22	
		* 2 5 5 8	ė	CF3	ĺ		NO2	NO ₂	-	NO ₂	Š	δÕ		Š	Š			Š	represent	3 (CH ₂) ₁ .	.	
45		3 (CH ₂)	7	z	z	z	z	z	z	z	z	z	z	z	z	z	z	Z	epr	£-Ÿ	-4	
		R3 X1 A 4 CH2)M-C-(CH2)M-C R4 X3	>	S ₈	CR6	S. Be	CR6	ဌ	ဗ်	8 8	CR ₆	CR ₆	S. Be	Д 8	CR ₆	ဗီ	S. Re	క్ర	lls r	R3 - - - - - - - - - - - - - - - -		
		(CH ₂	⋖	(2)	(2)	(2)	(2)	(2)	8	(8)	8	8	8	8	3	8	(2)	8	nera	<u>ن</u> ا	•	
50			혛	92	22	78	62	80	<u>-</u>	82	83	2	85	98	28	8	68	8	.Numerals	<i>a</i> ≯.	•	

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10	
15	
20	
25	16 7
30	Table
35	
40	
45	

!	#1	5	<u>, </u>	<u></u>	<u></u>	<u></u>	5	75	7.	<u>, </u>	<u>, , , , , , , , , , , , , , , , , , , </u>	<u></u>	<u></u>	<u></u>	<u></u>	5
	salt	H	HC	HC	HC	Ę	豆	걸	HC	모	豆	포	오	皇	모	포
	P _S	I	I	I	I	Ξ	Ξ	=	Ξ	Ξ	Ξ	듸	Ξ	Ξ	エ	듸
R 8	Ε	٥	۰	0	0	٥	•	2	<u> </u>	<u> </u>	•	<u> </u>	٥	0	<u> </u>	의
470	4	Ξ	Ξ	I	Me				I	I	I	Ξ	Ξ	I	I	Ξ
R ₈ A-2 (7)	Яз	Me	Œ	Pr	Me	-(CH2)5-	—(CH ₂)3—	-(CH ₂)4-	I	I	I	I	н	I	сн ₂ он	СН2СН2ОН
4/2/20	•	0	0	0	0	0	0	•	0	•	0	0	0	0	0	•
2-4° ©	ď	I	Ξ	Ξ	H	I	I	I	I	I	Me	-(CH ₂) ₃ -	-(CH ₂)4-	-(CH ₂) ₆ -	I	Ξ
₹,	R ₁	I	I	I	H	H	н	Ξ	Me	ũ	Me	5)	Н)	Н)—	I	I
3 F R8	Substitution position of We	3	3	3	3	3	3	3	က	3	3	က	3	3	. 3	9
	x4.5	6-н	6-н	Н-9	Н-9	Ь-9	Н-9	Н-9	6-н	6-H	6-н	Н-9	Н-9	6-н	н-9	Н-9
₹ >- €	x3.5	5-H	У- Ч	Н-5	5-H	Н-5	8-H	9-Н	H-6	5-H	Н-5	5-H	н-5	9-H	Н-9	S-H
4 6	x ⁵ ,5	4-H	4-CN	4-CN	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H
R8 1	x1.5	2-H	5-Н	2-H	2-H	2-H	2-H	2-H	2-Н	2-H	2-OMe	2-OMe	2-H	2·H	2⋅H	2-H
R ₈ R ₇ R ₇ R ₇ R ₇ R ₉	Rg.1	6-OMe	9MO-3	6-OMe	6-cyclobutyfthio	6-cyclopentylthio	6-cyclohexylthio	6-OMe	8WO-9	9WO-9	9WO-9	6-OMe	9WO-9	9МО-9	H-9	Н-9
3-4	Rg 1	5-H	9-H	5-H	5-H	5·H	5-H	5-H	5-H	9-H	5-H	5-H	S-H	F.	S-H	5-H
4 4.6.1.∨	R7.1	4-H	4-H	±	4-H	1 +	±	Ŧ	Ŧ	4-H	4.H	±	1.4 I	H-4	H-4	4.H
× × × × × × × × × × × × × × × × × × ×	tution on of A	2	2	2	2	2	~	2	2	2.	2	2	2	2	2	2
× ŽEŽ X	S _o		20N	NO ₂	NO ₂	δN	δ	δN	δ _N	δ N	လို	Ş	နှ န	S S S	ဂ္ဂ	NO ₂
(CH;	Z	z	z	z	z	z	z	z	z	z	z	z	z	z	z	z
ά <u></u> −ό−α	٨	9 _H O	СР6	CR6	CR6	CR6	CR6	CR6	CR6	CRe	CR6	C.R.	CR6	CR ₆	CR6	CR6
(CH ₂	٨	(2)	(2)	<u>@</u>	2	2	2	<u>@</u>	2	8	ହ	3	8	2	(2)	(2)
R2 X-1 X2 H2 X-(CH2)n-6-(CH2)m3 X4 16 R4 X3 X4 (1)	Er Ko.	91	92	93	94	95	96	97	98	66	100	101	102	103	104	105

*I:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.

			salt	亨	SHCI	Ş	Ë	2HCI	Ş	Ę	2HCI	HCI	Ę	ᅙ	亨	ᅙ	Ş	Ë	!			
5			P _S	I	I	н	н	x	I	I	н	н	н	Ϋ́	ŭ	'n.	A c	B2	!			
		8	E	o	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
10		E 22 E	4	I	I	н	H	н	I	I	н	н	I	I	I	I	I	I				
		4	જ	Ξ	I	I	н	н	н	н	н	H	Ή	I	I	H	Η	н	employed.			
_		R B	٥	٥	0	0	0	0	0	0	0	0	0	0	0	0	0	0	empl			
15		£ 2-29	P ₂	Ξ	I	I	I	Ξ	Ι	¥	н	Ŧ	I	Ξ	Ξ	Η	I	I	(2)-(1)			
		8g 4g	P.	Ξ	I	H	I	I	I	Ι	I	Ξ	I	I	I	H	I	н	of (2)			
20			Substitution position of W	e .	8	6	3	6	3	3	3	3	3	3	ဂ	3	3	3	formulas c			
		8 5 6 9 8 8	X4.5	Ŧ.	H.	н-9	H-8	Н-9	6-Me	H-9	H-8	Н-9	Н-9	Н-9	H.	6-H	н-9	Н-9	al for			
25	∞	\$ - \$	x3.5	H.S.	H-S	S-H	5-H	뚱	5-Me	H-5	5-87	5.H	5-н	5-H	5-H	5-H	F.S	9.H	structural for benzene ring			
	Table	- 6,	x2.2	4-Ph	4-H	4-H	4-H	± 4	H-4	4-Me	1. 1.	1 4	H-4	H-4	4·H	4-H	1.4 T.	4-H				
30	Ta	(a) - (c)	x1.2	2-H	2-H	2-H	2-H	2-H	2-H	2-146	2-H	2-H	2-H	н-2	2-H	H-2	2-H	2-H	in the			
		4 2,4,₹″	R ₉ *1	6-NO ₂	6-OM6	60M9	ij	6-Et	6-01/46) FE	H-9	H.	H-9	6-OMe	6-Ме	6-Et	6-OE1	Н-9	l .			
35		8 - 5 8 6 - R9	R8.1	S.H	S.H	5.H	S-H	5.H	5.H	5.H	H-4	S-OEt	4-NO ₂	5-H	S-H	S.H	r.	S.H	positions positions			
		E + ~ @	R7.1	4-OMe	Ŧ÷	#÷	2-H	2.H	2.H	2-H	2-Me	2.H	2·H	Ŧ.	4-H	H.A	H-4	H-4				
40		×	Substitution position of A	2	2	2	4	4	4	4	5	4	5	2	2	2	2	2	substitution substitution	Ę	. ~	
		× \$ 1 × ×	æ	I	A	СНО	H ₂ O2	CONH ₂	CO2Me	S	CF3	20 ₂	r	2 So	2 0₹	2 0€	20 №	ş	sent s		.H2M-N	
4 5		(CH2) (E)	2	_	z	z		z	z	z	z	z	z	z	z	z	z		epre	નું-	ب الم	2
		ųγ−ų.	>	CR6	CR6	CR6	S _R	S. Se	CR ₆	CR ₆	CR ₆	S. B.	CR ₆	S. Ro	ပ် မ	S B	SR		als r		CH2)m.	
		Ą	⋖	(2)	8	(2)	(2)	8	8	2	(2)	2	8	8	8	(2)	8	8	mera		Ť	
50		R1 X2 R2 X + CH2)II - C + CH2)III + CH2)III + CH2)III + CH2)II +	Er. No.	106	107	108	109	110	111	112	113	4.	115	116	117	118	119	120	*1:Numerals represent *2:Numerals represent	£-	≥. *	

				salt	豆	HCI	Ž H	Ş	호	ÖH	豆	Ş	Š	ΗĊ	D.	할	НСІ	H	豆] · · · ˈ	:		•
	5			P.	CO2Me	COZEL	I	I	Ξ	I	I	r	I	I	I	Ŧ	н	I	I				
				ε	0	0	0		0	0	0	0	0	0	0	•	0	0	-				
			8	2	Ξ	I	₩.	I	I	I	r	I	I	Н	H	I	Н	I	I	1			
	10		# F E	P3	I	Ξ	Me	СН2ОН	CH ₂ Br	I	Ξ	Bn	СН2СН2РҺ	СН2ОН	I	x	Ŧ	r	I	employed.			
			æ	c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	di			
	15		- 27°	82	Ξ	H	I	x	I	I	I	I	Ξ	H	н	Ξ	I	I	I				
			22	R	Ŧ	I	н	×	н	I	r	I	н	н	н	H	×	I	CH2CH2F	of (2)-(7)			
	20		8 8 8 6 E	Substitution position of Po	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	structural formulas o			
	<i>25</i>		8 - 5 - 8 - 8 - 8 - 8 - 8 - 8 - 8 - 8 -	×.	Ŧ ø	H-9	H-9	Н-9	Н-9	Н-9	H-9	6-H	H-9	H-9	6-NO ₂	H-9	Н-9	H-9	H-9	al fo	,		
			\$ - \$	×3.5	S. H.	5.H	5-Ph	H-5	H-S	H-9	H-\$	9-H	H-S	5-H	H-5	.н-\$	9-H	H-S	9-H	uctur	 		
(30	Table 9	8 A= 1	x2.5	4.H	4-H	H-4	4-CONH2	4-H	4-H	4-H	4·H	4-H	4-H	4-H	4-0Me	4-NHAC	H-4	4-CONH2	the str			
		Tal	- E	x1.5	5-Н	2-H	2-н	4-5	2-Me	2-Me.	2-сн ₂ он	2·H	2-Me	2-H	2-H	2-CI	2-H	2-Me	2-H	ii e			
	35		ନ୍ଧି ନ ଜୁନ ଜୁନ	.ea	6-SMe	6-SEI	9WO-9	9MO-9	9₩0-9	9 WO-9	8-OM8	6-OMe	9₩-9	6-Me	6-Me	6-Me	6-OMa	6-Et	6-Er	positions positions			
			- S - 5	. 8g	5.H	5·H	5-H	5-н	5-H	5-H	5-H	5-H	5-H	5-Н	5-H	5.H	5-Н	5.H	5-H	2, 2	,		
			* A # ~	R ₇ .1	Ŧ	÷	4-H	4-H	4.H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	H.4	tio tio			
	40		% =	whatitution osition of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	substitution substitution	ď	<u>.</u>	22
	45		R3 X1 X R2 V (CH2)n - C-(CH2)n - 4 X3 X R4 X3 X	Re	NO2	ZON	NO2	NO2	NO2	NO2	NO ₂	СО2Н	СО2Н	СО2Н	CO2Me	СО2Мв	N СО2Мв	СО2Мв	N CO2Me	represent represent		*: W = -(CH2)m - \$-(CH2)n -1	
			3 1 4	2	_	z	z	z	z	z	z	z	z	z	z	z	_	z	_	repr	. Æ-	- ¦-	Ŗ
				٨	CR ₆	CR6	CR ₆	CR6	CR6	CR6	CR6	CR ₆	C.R.	8 8	CR	CR ₆	ဗ္ဗ	S. Re	CR ₆	als als		СН2)ш	
	50		<u>5</u>	٧	(2)	2	2	<u>8</u>	(3)	(2)	<u>(2</u>	8	<u>@</u>	2	(2)	(2)	8	(2)	(2)	mer		Ţ	
				Er. No.	121	122	123	124	125	126	127	128	123	130	131	132	133	134	135	*1:Numerals		≯ ∵	

			salt	2HCI	2HCI	2HCI	2HCI	2HCI	ᅙ	귳	亨	ᅙ	ξ	Ď.	ᅙ	.: E:	Ϋ́	HC.			
5			R _S	7 H	Н 2	H Z	Н 2	Н 2	ı	± =	r	Ŧ	I	r	CHO CHO	ı	ı	<u>+</u>			
5			E	-	0	0	0	0	0	-	-	1	-	_	0	0	0	0			
		6	2	r	I	r	r	H	Y	r	r	r	r	r	r	r	н	H			
10		A S	F3	H	H	I	H	I	н	ı	I	I	I	ı	I	H	н	x			
		E E	_ c	1	1	-	1	1	1	0	0	0	0	0	0	0	0	0	.		
		¥	R2	H	н	I	н	н	I	ŗ	r	I	I	I	ı	r	н	r	employed		
15		A S	R ₁	Ŧ	н	H	H	H	I	I	I	H	r	r	r	×	н	H	emp		
		# ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° °	Substitution position of We	2	2	2	2	2	2	4	4	4	4	4	3	3	3	3	(2) - (7)		
20		S. R.	2 Subs	_	_			_	_		_								Jo		
		E _ E E	×	Н-9	Н-9	Н-9	н-9	H-9	н-9	H-9	H-0	Н-9	H-9	Н-9	H-9	H-9	н-9	H-9	las		
		£ 3	x3.5	5-H	9-Н	9-H	9-H	5-H	Н-6	H-S	F.F	5-H	5-H	5-СНО	5-H	5-H	5-H	5-H	formulas	n.	
25	10	(a)	x2.2	4-H	4-H	4-H	4-H	4-H	4-H	3-н	¥.	3-со2Ме	3-CONHMe	3-н	4-H	4-H	4-H	4-H	structural fo benzene ring.		
30	Table	F8 A B A B	x1.5	3-H	Э-Н	Э-Н	3-H	2-H	2-H	2-H	з-созн	2-H	H-2	Б-5-	5-H	2-H	2-н	2-H	the stru the benz		
	Ţ	3-5	R ₉ ·1	⊌ МО-9	13-9	Н-9	Н-9	Н-9	6-F	6-Br	H-0	н-9	F.F	н-9	6-OMe	6-ОМе	6-Ме	e-Et	ää		
		4	Rg.1	Н-9	H-9	Н-6	F-H	H-9	4-H	4-H	H-4	4-H	H-4	4-H	4-H	4-H	4-H	4-H	tions	1	
35		(3) - (5)	R7.1	2-CONMe2	2-CONHMe	2-NHAC	2-NHCO2M8	2-NHBz	2·H	2-H	2·H	2-H	2-H	2-H	Э-Н	3-Н	3-Н	3-H	ubstitution positions		
40		7 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -	Substitution position of A	4	7	4	4	4	5	5	5	S	S	S	2	2	2	2	ubstitution ubstitution		تر ر
		× × × × × ×	Re	H	I	I	I	I	NO ₂	NO2	NO2	NO2	NO2	NO ₂	I	I	Ι	I	ויי מין	,	2)n-N
45		H2)4	z	z	z	z	z	z	z	z	z	z	z	z	z	0-N	012	0-N	rese	5	<u>\$</u>
		£-∳-4 €	>	CR ₆	CR ₆	CR ₆	န္	9. 9.	မ္မ	န်	8	CR6	CRe	CR6	CR6	CR ₆ NO	CR ₆	CR ₆ N→0	s rep	,	-5 -5 -4 -4
50		(CH ₂)r	V	(2)	(2)	(2)	8	(2)	8	(2)	8	(2)	(2)	(2)	(2)	(2)	(S)	8	eral) 	3
50		R ₃ X ₁ X ₂ R ₂ X - (CH ₂)n - (-(CH ₂)m + (-(CH ₂	Er. No.	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	*1:Numerals represent	:	W = _(CH ₂)m_C(CH ₂)n_=

SHC 2HC

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-(CH₂)₂--(CH2)3--(CH2)4-

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I I

-(CH₂)₃--(CH₂)4-I I I

0 0 0 0 0

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6 ၉ n e က

H-9

5-H

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| |-|-2-H

g.

5.H 5-H

A T 4.H

N

CH CO2H

CR CR6

8 (2)

161

160

F. H-9 F.

5.npr 5.

4·H 4-H

9-NHubr

7 8 N

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162 163 164 165

(2) CR₆ CH CO₂H

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			salt	亨	호	호	2HCI	SHC	2HCI	ᅙ	Ş	Ş	호	[
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		A R &	33	ī	Ξ	I	Ī	Ī	I	I	ī	ī	-(CH ₂) ₂ -	į
10		E - E	-	0	0	0	0	0	•	0	0	0	0	,
15		5 A A A	R ₂	I	Ŧ	Ξ	CH ₂ CH ₂ F	СН2СН2СІ	СН2СН2Вг	Ξ	I	I	Ŧ	
15			R,	I	I	I	CH2CH2F	СН2СН2СІ	СН2СН2Вг	I	I	I	H	2
20		# 2 - # 6	₩ £	ε	3	ε	3	ε	6	3	9	3	3	٠
		₹ .	X4.5	H-9	6-Н	Н-9	е-н	6-H	H-9	6-н	H-9	6-H	Р-9	7
25	11	* - 3	X3.5	Н-9	5.H	5.H	₽-5	5-Н	Н-9	5-H	H-S	S-H	5-Н	7
		₹ % %	X2.2	4-H	4.H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	007
30	Table	(S)	x4.2	5-Н	5-н	2-H	5-н	2-H	5-н	5-н	5-Н	2-H	2-Me	7.0
		# \$ * \$ *	Rg-1	6-Me	6-Et	6-OMe	H-9	Н-9	Н-9	Н-9	Н-9	Н-9	6-Ме	000
35		2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -	Rg.1	5-н	5-H	5-H	5-NHMe	5-NMe2	5-NHEI	5-H	5-Н	5-H	5-H	7
		\$ * * * * * * * * * * * * * * * * * * *	R7.1	4-H	4-H	H-4	H-4	4-H	H-4	4-SMe	4-SEI	4-SnPr	4-H	7.
40 .		1CH2)n-C-(CH2)m-1 R4 X3 X4 X3 X4 (1)	Substitution position of A	2	2	2	2	2	2	2	2	2	2	ç
		* <u>Z</u> EZ~	æ	NO2	20N	NO2	NO2	NO2	NO2	NO2	NO ₂	NO2	н⋜оэ	700
45		3 (CH ₂)	7	ᆼ	НЭ	нэ	СН	СН	СН	СН	нэ	СН	НS	2
		E-0-4	>	CR ₆	CR ₆	CR6	CR ₆	CR ₆	CR6	CR ₆	CR6	CR ₆	CR ₆	ģ
		(CH2)	4	<u>(2</u>	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	Ę
C0		7	$\overline{}$	_					_	_			_	_

Ex. No.

151

153 154 155 156

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structural formulas of (2)-(7) employed. benzene ring. *1:Numerals represent substitution positions in the *2:Numerals represent substitution positions on the R3 = -(CH2)m-¢--(CH2)n-N

6-SEt

F.

2.H

4-H

N

5-H

4-NHEI

5-H

ပ္ 6-Br

¥. 5-H

4

сн созн CR6 CH CO2H

CR

(2) 8

2-NHBn

4

5-H

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22

				salt	2HCI	2HCI	Ξ	호	Σ̈́	호	Ę.		Ş	豆		ᅙ		HC	ĦĊ				
5				R _S	I	I	Ŧ	I	Ξ	I	Ξ	I	Ŧ	Ξ	I	I	н	I	Ή				
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10		4 F	F-E	8	_	<u> </u>				_		_	_	_	8		-	_		ġ.			
10		A		-	I	I	I	I	I	I	H	I	Ι	I	Me	₩	Мв	-Bn	СН2ОН	employed			
		3 R8		<u>د</u>	0	°	0	0	0	0	0	•	0	0	0	0	0	0	0	emp			
		1 7 mg	z & @	82	Ξ	=	I	I	H	I	Ξ	Ξ	I	I	Ξ	Ξ	X	H	Ξ	1			
15		A STATE OF THE STA	<u>. </u>	Œ.	I	r	I	Bn	СН2СН2РҺ	I	I	Ac	r	Ŧ	r	I	Bz	Ξ	I	of (2)-(7)			
20		F. B.	z— & @	4 6	3	ε	3	3	3	3	3	ဧ	8	3	3	3	3	3	3	structural formulas o			
		₽ 		X4.2	H-9	6-н	H-9	н-9	9-Н	н-9	Н-9	Н-9	H-9	H-9	H-9	Р-9	Н-9	н-9	н-9	forr			
		**************************************) _ (9)	x3.5	5-H	5-H	S.H	S-H	S-H	8-H	5-H	S-H	5.H	S-H	5-H	5-H	5-H	5-H	5-H	ral			
25	12	**************************************	\$-€		-1-yl	-1-yt												_		structural fo benzene ring.			
	Table 1	78 5 79 79 78		x5.5	4-pyrnolidin-1-yl	4-pyrrolidin-1-yl	H-4	4-H	4-08n	4-H	4-H	4-H	1.4	4·H	4-H	4-H	4-H	4-H	4-H	the			
30	Ţ	£ 24	} >-@	x1.5	2·H	2·H	2-OMe	2-OEI	2-H	2.F	2-CI	2-Br	2-H	2-H	2.H	2-Н	2·H	2-H	2-H	s in			
		4		Rg.1	6-Me	6-Ei	6-OMe	6-Me	6-Me	6-Me	6-Me	6-Me	6-Et	6-OMe	6-Me	6-Me	6-Me	6-Me	6-Me	positions positions			
35		3 4 4 8 4 4 8 4 4 8 4 4 8 4 4 8 4 4 8 4 4 8 4 8 4 8 4 8 4 8 4 8 4 8 8 4 8	2-8	Rg*1	H-S	н-5	H-6	S-CONH2	5-CONH2	S-CONMe2	5-CONMe2	S-H	S-H	5-н	5-Н	S-H	H-S	S-H	9-H				
40		A.	× × × × × × × × × × × × × × × × × × ×	R7.1	4-H	4-H	4.H	4·H	4-H	4-H	4-H	4-NHAC	4-NHAC	4-NHAC	4-NHBn	4-NHBn	4-NHBz	4-H	4-H	substitution substitution	_	•	
		× × × ×	Ž-, "	Sebstitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	ľ	4	بن ا ا	•
45		CH2)	R2 R4 X3)	R ₆	сн созме	сн сожи	сн соъме	H	Ξ	Ŧ	Ξ	I	r	н	н	Ξ	H	CF3	CF3	represent represent	F-3	(CHS) 	*
		£-Ÿ	-8 -2	7	EH CH	_	СН	СН	НЭ	нэ	СН	нэ	H U	СН	СН	СН	СН	СН	СН			Į,	-
		Ή2)r	,	\	СЯ6	СЯ6	СЯв	СВ6	CR6	CR6	cR_6	CR6	CRe	CR6	CRe	CR6	CR6	CR6	CR6	*1:Numerals *2:Numerals	į	(CH2) × : ★	
50		٦ بخ		٧	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	N LEM	•	; } -	
		ď Ì	R.	자	166	167	168	169	170	171	172	173	174	175	176	122	178	179	180	*1:		* *	

			salt	Š	Ş	ᅙ	2HCI	2HCI	2HC	2HCI	2HCI	2HCI	Ę	Ξ	Ä,	ΗĊ.	HC:		·
_			P.	I	Ξ	I	I	H	Ξ	I	I	I	I	I	Ξ	Ξ	I	Ξ	
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		* ° °	Æ	Ŧ	I	н	H	I	I	I	I	I	I	Ξ	I	I	Me	Ме	(2) - (7)
20		S B	Selectivation of partition of	6	9	9	3	3	3	3	3	9	3	3	3	3	3	3	as of
			X.2	H 0	Н-9	H-9	8-NO ₂	ноч	H-9	Н-9	Ŧ9	H-0	Н-9	Н-9	H-9	H-9	H-9	6-NO ₂	ormula.
		4°	x3.5	F.H	5-CN	5.H	5.H	S-H	5-H	9-H	S-H	5-H	5-H	5-H	9-H	5-H	5-H	5-H	1 f
25	13	= 3 × B	x2.5	4 HO4	4-H	Ŧ	H-4	Ŧ	H-4	4-CH ₂ Ph	4-СН ₂ ОН	H.	H-4	H-4	H.	H-4	H-4	4-H	structural formulas benzene ring.
30	Table	8 € 1 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	x1.5	2-H	2-H	5-н	2·H	2-H	2-H:	2-H	2-H	2-CH ₂ OH	2-H	2-H	2-H	20H	S-CN	2-H	the
35	Ţ	7 Re R7 Re 7 Re 7 Re 7 Re 7 Re 7 Re 7 R	R ₉ .1	6-cycloburyl	6-cyclopentyl	6-cyclohexyl	H-9	H-9	H-9	Н-9	H-9	H-9	6-cyclobutylthio	6-cyclopentylthio	6-cyclohexylthio	Н-9	6-H	Н-9	positions in positions on
40		2 - 0 B	. Rg .	9-H	H-8	H-S	9-H	H.S	S-NHCOMe	S-NHCO2Me	5-СНО	5-H	H-S	H-S	9-H	9-H	9.H	5-H	substitution graphs and substitution graphs and substitution graphs and substitution graphs and substitution graphs are graphs
		λ = α,	. A	Ŧ	4-H	4-H	4-H	H-4	H-H	4-H	H-4	Ŧ.	4-H	4-H	4-H	4-H	4.H	H-+	ubs R
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R ₁ N ⁻ (CH ₂) ¹¹⁻ C ₁ C(H ₂) ¹¹¹ N ² N ⁴	E	R8*1	H-S	H-9		NO-S	S-CN	S-CN	H-S	5-н	5.H	H-4	н-4	4-cyclopropyl	4-cyclobuty1	4-cyclopentyl	4-cyclohexyl
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30	Table 1	R ₈ A ₂ 3 A ₃ A ₄ 3	x3.5	5-H	9-н	5-CONH2	5-CONHM8	S-CONHEL	9-H	5-н	5.H	9-H	Н-6	Н-6	9-H	5-CH ₂ Br	S-CN	5-CF3	the struc)	
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3 + 4 RB 1 RB (5)	Substitution position of 80	3	3	6	6	3	6	8	ဗ	8	3	3	3	3	3	3
FB FB AF	X4,2	H-9	Н-9	H-9	H-9	H-9	6-H	н-9	H-9	Н-9	В-Н	6-СО2Н	в-соъме	6-CO2E1	Н-9	H-9
	z. [£] x	н-ѕ	H-S	S-H	H-S	H-6	9-H	S-H	5-NO2	5-NO2	20N-2	5-H	H-6	H-S	H-9	Н-5
}68 4.	X2.2	4-OMe	4-0Et	4-Onpr	4-OiPr	H-4	4-H	4-H	H-4	H-4	4-H	H-4	H-4	4-H	4-NH2	4-CONH2
2 - E	x1.5	2-H	2-H	2-H	2-H	2-Me	2-EI	2-upr	2-H	2-H	2-H	2-H	2-H	2.H	2-H	2-H
₹	R ₁₃ *1	Ξ	I	Ϋ́	I	Ŧ	I	ũ	I	I	ubc	I	I	I	I	Ξ
2 - 3	R ₁₂ *1	9 // -S	S-Et	S-npr	3-ipr	5-OMe	SOE	5-OnPr	5-SMe	5-SEI	5-S ⁿ Pr	5-H	F.	7.	H.S.	£.
4	R11.1	4-H	4-H	4-H	4-H	4-H	H-4	4-H	4-H	4.H	4-H	4-H	4.H	H-4	4-H	4.H
× - × - × - × - × - × - × - × - × - × -	Substitution position of A	2	2	2	2	2	2	2	2	2	. 2	2	2	2	2	2.
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g-0-π 0 • Ξ	Ţ	CR6	CRe	CR_6	CRe	ည	S _B	CR_6	c _R e	CR6	CR6	СЯв	CR6	CR6	CR ₆	CRe
(CH ₂)	∢	(2)	(2)	(2)	(5)	(2)	(2)	(s)	(2)	(2)	(s)	(2)	(2)	(2)	(2)	(2)
œ œ	Er. Ko.	256	257	258	259	260	192	262	263	264	265	592	267	268	269	270

#2:Numerals represent substitution positions in the structural for #2:Numerals represent substitution positions on the benzene ring.

R3

R3

R1

*:W = -(CH2)m - C-(CH2)m - N

							_	-		_				<u>ئىت</u> ىم	<u>.</u>	<u>.</u>						
			salt	모	귳			2HC	2 FC		2HCI		2HC	2HCI	Σ.	ži.	25.	2HG				
5			Ą.	CO2Me	COZEI	I	I	I	I	Ξ	I	I	I	π	Ι	Ξ	I	I				
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10		8 R	ð	I	I	I	Ξ	I	We	I	I	Ι	I	I	I	СН2СН2Вг	I	I				
		88 ↑	R3	I	Ξ	I	I	I	Me	I	I	I	I	1	н	СН2СН2ВГ	r	I	employed.			
15		~/ w	c	-	-	-	=	-	=	0	0	0	0	0	0	0	0	0	8			
		4 2 6 0	&	π	Ξ	I	Ξ	2	I	I	π	н	I	н	CH2CH2CI	н	I	Ŧ	(2)-(2)			
20		E - E - E - E - E - E - E - E - E - E -	ę.	Н	Ή	Ą	28	Me	I	‰E.	Ξ	CO21Bu	Ξ	н	CH2CH2CI CH2CH2CI	Ξ	I	I	las of			
		8 4 6 9 4 2 4	Sectification of the section of the	4	4	4	4	4	4	9	9	9	9	9	9	9	9	9	structural formulas benzene ring.	,		
25		1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	×4.5	6-Н	н-9	H-9	H	Ŧ	H-9	H.S.	S.H	5.H	5.H	5-H	5-H	5-H	F.S	5.H	structural fo benzene ring.	,		
	19	3-5-S	×3.5	5-H	5-H	H-S	7	5.H	F.	±	±	4-H	Ŧ	4-H	4-H	4-H	# .	4-H	uctu			
30	Table	R8 8 89 AE.	x2.5	3-H	3-Н	3-H	H-6	3.H	H-C	H.C	H-6	3-NHAC	3-NHBz	2-CONHMe	э.н	3-н	H-C	3.H	the the			
	г	3 - 5	x1.5	2.F	2-CI	2-Br	2-H	2.H	2-H	2.H	2-H	2-H	2-H	2-H 2	2-H	2-H	2-H	2-H	4 6	i		
35			R ₁₃ .1	Ξ	H	Ac	Ξ	±	82	I	I	CO2Me 2	ı	1	CO2Et 3	I	I	CO2 ^{tBu}	sitions	 		
		4 - (S)	R ₁₂ *1	Ь-8	Н-5	5-NHAC	5-NHB2	5-H	5-H	S-CONHE!	S-CONHUPL	P-9	5-H	H-S	5-H	9-H	5-H	5-H	substitution positions in substitution positions on	in		
40		R ₁ X ₁ X ₂ X ₁ X ₂ A ₂ X ₄ B ₁ A ₂ X ₄ B ₁ A ₂ X ₄ B ₁ A ₃ X ₄ B ₂ X ₄ B ₂ (1)	R ₁₁ *1	2-СНО	2-СНО	2-H	2-H	2-CONH2	2-CONHMe	5-H	2-H	2.F	2-CI	2-Br	2-H	2-H	2·H	2-OH				:
45		X A THE SE	Statitation position of	4	4	4	4	4	•	•	4	4	4	•	4	•	4	4	*1:Numerals represent	. E-	(CH2)	_
		6 √- 6 €	Р6	I	Ξ	Ξ	H	I	н	н	Н	I	н	H	NHMB	NHE	JduHN	Ξ	repr	, &-	<u>ن - ر</u>	r.
		CH29h	-	S. B.	CR ₆	CRe	CR6	CRe	CR6	CRe	CR6	S _B	CR _B	CR6	CR6	CR ₆	CRe	CR ₆	*1:Numerals)	
50		Ž.	∢	<u>©</u>		<u>(2</u>)	(2)	(2)	(2)	(2)	(2)	3	(2)	(2)	(2)	(2)	(2)	(s)	ume.		'n ≥	
		£ £	ಭಕ	27.1	272	273	274	275	276	277	278	279	280	281	282	283	284	285	*1:N *2:N		*	

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[数20]	6											C			ć				
a a	CHD	<u> </u>	N-(CH2)n-(-(CH2)m-(-)-(CH2)m-(-)-(-(CH2)m-(-)-(-)-(-(-)-(-)-(-)-(-)-(-)-(-)-(-)	× × × × × × × × × × × × × × × × × × ×	4	- 2	78 5 79 A			4 5 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	W B B C C C C C C C C C C C C C C C C C	2-6	S Ag	A= 2	F-83	¥	Sec.	E-1-7-E	. ec . vs
Er. No.	<	-	Substitution position of A	A ₁₁	R12 1 R13 1	R ₁₃ *1	x1.2	x2.5	x3.2	x4.2	Substitution position of We	P. (5)	P2	2	H ₃	4	ε	െ	salt
286	(5)	z	2		H-8	Ma	_	4-H	5-H	H-9	3	I	I	0	Me	I	0	I	HC
287	(2)	z	2	4-NO2	5-H	I	2-E1	# .	5.H	Ŧ.	3	₩	Ξ	0	I	I	0	Me	нсі
288	(2)	z	2	4-CO ₂ H	S.H	Ξ	2-H	4-nPr	F.F	H-9	9	I	Ξ	0	ĒÌ	н	0	I	нсі
289	(3)	z	2	4-CO2H	5-H	ធ	2.H	4-lpr	F.H.	H.9	e	ij	I	0	н	H	0	ũ	HCI
290	(2)	z	2	4-CF3	5-H	Ξ	2·H	H-4	5-OMe	Ŧ.	3	Ξ	Ŧ	0	nPr	I	0	ェ	2HCI
291	<u>(S)</u>	z	2	4-CF3	5-H	Ξ	2.H	H.4	s-OEt	H-0	3	υbr	H	0	x	I	0	¥	Ę
292	છ	z	2	4-CO2M8	F.F	ubi	2.H	H-4	H.º	6-NHMe	6	н	H	0	н	н	0	I	2HCI
293	(5)	z	2	4-CO2Me	F-R	Ξ	2.H	4-H	5-H	6-NHEt	3	-CH2CH2-	-21	0	н	н	0	B2	Ω H
294	3	z	2	4-CO2Et	5-H	Ξ	2-SMe	H-4	5.H	Ŧ	9	I	H	0	—сн ₂ сн ₂ —	_	0	I	HC
295	(3)	z	2	4-CO2E1	H.S.	ă	2-SEI	H-4	5-H	6-н	3	Ą	Ξ	0	I	I	0	I	
296	(6)	z	2	4-CN	9-H	Ξ	2-H	4-0H	5-H	6.H	3	I	Ξ	0	СН2СН2Е	I	0	I	Ä

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*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed *2:Numerals represent substitution positions on the benzene ring.

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4-NHAC 4-NHMe

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$$*$$
: W = -(CH₂)m- $+$ -(CH₂)n-N

		salt	2HCI	2HCI	2HCI	HC	Ĕ	Ξ	2HCI		2HCI	SHCI	2HCI	2HCI	HC	HCI	亨	
5		R _S	Ξ	I	Ŧ	СНО	CO2Me	COZEI	¥	H	Ξ	н	н	н	Ŧ	H	I	
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15	£ 6 €	_	0	0	0	[1	Ξ	0	0	-	=	0	0	0	0	0	0	(2)
	. R8	R2	CH2CH2CI	Ι	СН2СН2Вг	н	I	Ι	×	ng ₁ ZOO	I	вМ	н	н	н	н	×	of (2)-
20	4 5 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -	Æ	CH2CH2CI	Ξ	CH ₂ CH ₂ Br	H	I	Ξ	x	ဂရာဇီဝ၁	Ξ	Me	I	H	н	x	I	formulas ng.
25	8 2 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Sanditedias parities of	3	က	3	7	4	4	4	~	2	2	2	2	3	3	က	structural fo benzene ring.
8 21	- 01 0	×4.2	6-NO ₂	6-NO ₂	9-Н	Н-9	H.	F.	есно	H-9	H-9	Н-9	н-9	н-9	50N-8	е-сно	H-9	structural benzene ri
% Table	F 8 5 8 9 6 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	x3.5	H-S	¥5	5-СО2Н	F.	H.	S-CN	F.	H-S	1-S	F-S	H-S	9.H	Н-S	Н-9	9-H	the
·	# * * * * * * * * * * * * * * * * * * *	x ₂ . ₂	H-4	4-H	H-4	з-соъме	3-CO2E1	3.H	H-E	H-4	4-CONHMe	H-4	4-CH2CI	4-H	4-H	4-H	H-4	positions in positions on
35	(2) - (2) - (3) - (4) - (4) - (5) - (5) - (5) - (5) - (5) - (6) -	x1.5	2.H	2-H	2∙H	2-H	2∙H	2·H	2-H	3-CONH2	Э-н	з-снъон	н-£	3-Н	2-H	H-2	H-2	
40	4 4	R ₁₃ .1	82	I	I	I	Ξ	CO2Me	I	I	Ξ	COZEI	Ξ	I	I	പുട്ടാ	I	substitution substitution R ₁
₩	×~-~×	R ₁₂ ·1	5-NMe2	S-NHE	5-NH ⁿ Pr	S-OH	S-OMe	S-OEI	S-Me	9-H	5-H	H.Q.	5-SMe	5-SEt	よ	5-H	5.H	1 7
45	H3 X1 X 	Schellifting R11"1.	4-H	4·H	4-H	4-H	H-4	4-H	4-H	2-Me	2-EI	2-nPr	2-H	2-H	4-Me	4-Et	4.nPt	represent represent R3 1 C (CH2)n-
	E-7-4 E	Settled is petitive of	2	2	7	2	2	2	2	4	4	4	4	4	2	2	2	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	-(CH2)n	-	z	z	z	z	Z	Z	z	z	z	Z	z	Z	N-0	N-0	Q Z	*1:Numerals : *2:Numerals : *:W * -(CH2)m
50	<u>,</u>	∢	(5)	(2)	(2)	3	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(5)	(2)	(2)	(2)	7 × ×
	# #	퍆츅	301	302	303	304	305	306	307	308	308	310	311	312	313	314	315	* \$2::

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			salt		Ξ		딮		HC	고 모	닺	2HC	SHC!	똤	2 1 2 1 2		SHCI	2HCI				
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20		6 5 5 − 8 €	F	CO2fBu	I	Ac .	I	Bz	н	I	н	Ξ	I	н	I	CO2Me	СН2СН2Вг	Ι	formulas c			
25		F8 5 A2 6 R9 A2	selective of selections of	9	9	3	6	9	9	9	6	3	ε	ε	3	3	3	6	structural for benzene ring.			
	22	\$ - \$	×4.5	F.	H.	H-9	H-9	Н-9	Н-9	F-H	H-0	F-H	Н-9	Н-9	H-9	Н-9	H-9	6-NO ₂	ructu			
30	Table	R8 − F89 A=	x3.5	F.	S.H	9-H	9-H	S-H	5.H	F-6	F.S.	S-NH2	S-NHMe	5-NHEI	9-H	9-H	9-H	S-H	the st			
	E	£ \$ - €	x5.5	÷	H-4	4-0Me	4-H	4-0Et	H-4	4-OnPr	H-4	4-H	H-4	H-4	4-SMe	4-SEI	4-H	I.	12 8			
		**************************************	x1.5	2·H	2-Me	2-H	2-E1	2.H	2-upr	2.H	2-H	2.H	2-H	2.H	2.H	2-H	2-H	7.H	positions positions			
35		7 HB 2 1 5 HB	%	6-Me	H-9	6-Et	H.	9-nPr	F.H	P-∪Bu	HO-8	6.H	H-9	H-9	H.	H-9	H.	6-Me	pos	1		
40		4	R ₈ -1	5.H	H-9	9-H	8.H	9-H	9-H	9-H	9-H	9-H	5-NH ₂	5-NHAC	S-NHBz	H-S	H-S	S-H	substitution substitution			
40		ZZ+Z & X - Z - X A - Z - A - B - Z - A - B - Z - B - B	R ₇ 1	2-NO ₂	2-NO ₂	2-CO ₂ H	2-CO2H	2-CO2Me	2-CO ₂ EI	2-CO2nPr	S-CN	2-CN	2·H	2·H	2-H	2-CONH2	2-CONHMe	2-H	ł.,		¥	
45		R1 X1 X2 H3 X1 X2 X4 X2 X3 X4 X4 X4 X3 X4	Section of position of	၉	9	6	က	9	3	3	9	9	6	3	3	3	3	6	represent	· E-	*: W = -(CH2)m-c(CH2)n	· 2 *
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		\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	S to																(2)	
20		88 8	Substitution position of W	*	4	7	4	7	7	9	9	ဖ	9	9	9	3	4	Ġ	as of	
		2 4 5 5 4 8 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	X4.2	нгоэ-9	6-CO2Me	6-00 ₂ E1	Н-9	6-Н	6-CO2NH2	H-S	9-H	5-CO2NHMe	5-cyclopentyl	5-H	5-H	6-Н	6-cyclohexylthio	5-H	structural formulas benzene ring.	
25	23	€ - €	x3.5	H.S.	H-6	H-6	S-CN	SF	S-H	H- ₩	H-A	Ŧ	H-4	4-H	4. H	5-H	5-H	4-Bn	ructu	
		4	x2.5	Ŧ	3-H	3-H	3-H	3-H	3-н	H.	3.H	H-E	3.H	Э-Н	3-H	4-H	H.E	3-H	ber	
30	Table	F 7 4 5 CO	x1.5	2.H	2-H	P-2	2·H	2-H	2-H	2-CI	2-СН2ОН	2-H	2·H	2-H	2-н	2-H	2.H	2.H	in the	
35		7 R8 7 5 2 2 6 19 A= 2 4 (2)	Fg.	a de	9-upr	e-nBu	Ŧ	H-8	Н-9	H-9	6-н	H-9	Н-9	6-pyrrolidin-1-yl	6-piperidino	6-cyclobutyl	H-9	H-9	n positions n positions	
			-Ba	9-H	9-H	S.H	50H	S-OMe	SOE	5-H	9-H	F.S	5-H	5-H	5-H	5.H	S.H	F.S	substitution substitution A ₁	
40		%	B7.1	2·H	2-H	2-H	2-H	2·H	2·H	2-SMe	2-Et	2-CF3	2-CF3	P-2	P-2	2-H	2·H	2·H	substi substi	2
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50		j)	٧	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	€	3	(4)	(4)	(4)	€	€	mer; mer;	
		e z	Er. No.	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	*1:Numerals *2:Numerals *2:W = -(CH ₂)m	

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of (2)-(7) employed *1:Numerals represent substitution positions in the structural formulas *2:Numerals represent substitution positions on the benzene ring.

*: W = -(CH2)m-¢--(CH2)n-!

		۲.	T ₌	Т	5	15	ਨ	15	<u>.</u>	-	5	15	1.5	Ι_	7.7	5	5	1			
		salt	웃		2HC	2HC	2HCI	2HCI	오	오	2HCI	2HCI	2HĊ	고 단	2HCI	2HCI	2HCI				
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10	E	2	I	I	I	I	I	I	Ξ	I	I	Ξ	I	I	I	I	I	ed.			
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15	4 N	R ₂	I	CO ₂ lBu	I	I	I	I	I	I	I	I	I	I	I	I	I	(2)-(7)			
	# 2	ď.	I	CO ₂ tB _W	I	Ι	I	I	I	I	ŭ	I	Ξ	I	I	I	I	as of			
20	4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 -	Schelletion position of	6	6	င	က	*	*	•	3	3	3	၉	စ	9	9	က	formulas	<u>.</u>		
25	8 2 - €	× 2.	6-H	H-9	6-CONH2	Н-9	H-9	H-9	Н-9	Н-9	H-9	Н-9	H-9	S.H	5-Н	5-H	H-9	structural for benzene ring	r		
s Table 25	Re 4 37	x ₃ .2	5.H	s-cozei	5-H	S-CONHIMB	5-pyrrolidin-1-yt	5-piperidino	Н-8	5-H	H-S	S-H	5-Br	4-СН2СН2Рћ	4-CH2(CH2)2Ph	H-4	S-H	the			
	4 	x ₂ .2	4-CO2H	Ŧ	4-H	H-+	3-H 5	3-H	3-н	4-H	4·H	3.5	3.H	3-H	3-H 4-	3-н	3-н	ions in			
35	8	x1.2	2-H ,	2-H	2-H	2-Н	S-CN	2-H	2-H	2-H	2-F	5-Н	2-H	2-H	2.H	2-H	2.H	positions positions			
	2 - 3	F. g.	£.	н-9	Н-9	6-Snpr	H-9	H-9	6-Me	Н-9	H-9	H-9	6-OnPr	8-OMe	9-н	6-NHMe	6-NHE	substitution			
40	₹	. _B	5.H	5-Н	5-SEI	5-н	9-H	5-Br	P-9	5-H	9-H	5-0EI	5H	9-H	5-H	9-H	9-H	stiti titi	!		
	× × × × × × × × × × × × × × × × × × ×	R7.1	4-Me	4-SMe	4-H	4-H	4 -F	4·H	4-H	4-H	3-OMe	3-H 5	3.н	3-NO ₂	3-н	3.Н	э.н			,×.	H ₂
45	R, N-(CH2)n-C-(CH2)m-1 R2 N-(CH2)n-C-(CH2)m-1 R4 X3 X	Schriftette perities of	9	3	3	3	က	3	3	3	4	4	4	4	4	4	4	represent represent		—(CH ₂)u–	
40	E-0-4 5	₹	z	z	z	z	z	z	N-0	0-N	z	z	z	z	Z	0-N	O-N		. Ε−		-₫
	H297	ם	z	z	z	z	z	z	0-N	0-N	z	z	z	z	z	0-N	0-N	*1:Numerals		*: W = -(CH2)m-C	
50	Ť Ž	4	(3)	(6)	ල	<u>0</u>	<u>(c)</u>	3	<u>e</u>	ල	ල	3	(3)	(3)	(3)	(3)	(3)	Nume		>	
	R R	ಭ್ತ	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	*1::	I	>. ★	

			salt	2HCI	2HCI	Ş	HCI	Ş	E C	2HCI	2HCI	2HC		ᅙ	HĊ.	空	•	ξ	İ		
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		£ 2 8 9	R ₂	ı	I	I	I	I	I	H	r	Ξ	H	Н	н	x	CO ₂ IBu	I			
20		R8 A= 2	Ä	Me	H	I	E	Τ	I	nPr	I	I	Ac	н	I	Ή	co ₂ lBu	r	of (2)-(7)		
			Substitution position of Pe	3	ε	3	8	3	ε	ε	3	3	E	3	3	3.	3	3	the structural formulas o		
25		H7 H8 2 2 2 4 5 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 4 6 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 6 4 9 9 6 4 9 9 9 9	x.2	H-9	Н-9	H-9	Н-9	н-9	Н-9	н-9	ӨМНМ-9	Н-9	н-9	Н-9	Н-9	н-9	Н-9	Н-9	structural fo benzene ring.		
	3 26	\$ - \$	x3.5	S-H	Н-9	9-H	5-H	H-S	9-н	5-NH2	5-Н	5-H	5-H	5-H	Ь-8	5-H	Н-5	5-H	ructu		
30	Table	7 R8 5 1-1 (3)	x ⁵ .5	4-Me	4-Ē	4-nPr	¥.	H-4	4.H	÷	4-H	Ŧ.	# .	4-H	4-H	£	4-0Et	4-0Bn	the st		
	E	A 2 6	x1.5	1-2	2·H	2·H	2-СН2ОН	2-СН2СН2ОН	2⋅H	2-H	2-H	2-NHEI	H-2	20	2-8r	2-OMe	2-H	2-H	ii 8		
35		7 R8 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1	R ₁₃ *1	Ŧ	Σ	Ξ	ū	Ξ	Jdu	I	I	Ξ	I	Ą	8	CO2Ma	CO,Et	CO2nPr	posit posit		
40		₹ ***	R ₁₂ '1	5-H	H-6	9-H	H-S	8-CO2H	S-CO2Me	5-CO ₂ E1	н-9	5.H	H-Q	H-S	H.	F.H.	5H	H-S	substitution positions substitution positions		
		× × × × × × × × × × × × × × × × × × ×	. R11.1	4-NO ₂	4-NO2	4-CF3	4-CF3	4-H	H-4	4-H	4-CN	4-CONH2	4-CONHMe	H-H	4·H	4-H	4-H	4-H		¥	2
45		R, X - (CH2) -	Substitution position of A	3	3	3	3	3	3	3	3	3	3	3	က	6	က	6	represent represent Ra	Ł	R.
		<u></u>	-	z	z	z	z	N	Z	N	N	Z	N	z	z	z	z	z		. W = -(CH ₂)m	
50)	0	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	9	9	9	9	ne ra	Ť	
		źż.	.	976	377	178	621	180	181	182	183	184	185	981	187	88	689	06	:Numerals :Numerals	≥	

			salt	호	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	HC.	ᅙ	2HCI	皇				
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		2	ε	0	0	0	0	0	-	1	0	0	0	•	0	0	0	0				
10		E	2	Ξ	I	н	H	н	H	н	H	H	I	I	Ξ	-CH ₂ (CH ₂) ₃ CH ₂ -	I	I	employed.			
		4 / 20 H	સ	Ξ	I	н	н	H	Me	н	н	н	н	I	н	-CH2	H	Ξ	l .			
15		2- a 9	_	0	0	0	1	1	0	0	0	0	-	1	1	1	1	-	(2)			
		R ₈ A-2	22	I	Me	I	I	r	r	СН2СН2Вг	I	I	н	π	2)2CH2-	I	н	I	of (2)-(7)			
20		E - E 6	R	I	Me	I	Ξ	Ι	I	сн2сн2вг	r	I	I	π	—СН ₂ (СН ₂)2СН ₂	н	н	н	structural formulas benzene ring.			
25		S S S S S S S S S S S S S S S S S S S	Sectification profition of	6	Б	е	4	4	4	4	6	8	9	9	9	3	e	4	ural f e ring	ı		
	3 27		X4.5	6-NO ₂	6-CO2Me	6-CO ₂ Et	H-9	H-9	H-9	Н-9	H-9 ·	Н-9	5-СНО	9∙H	Н-S	H-9	H-9	H-9				
30	Table	2 × 6 × 5 × 6 × 6 × 6 × 6 × 6 × 6 × 6 × 6	x3.5	5.H	5.H	5.H	5-CONH2	S-CONHMe	S-CONHEI	5.H	9-H	H-6	4-H	4-NHCO2Me	4.H	5-H	H-9	5-H	is in the			
35		8 8. 1 Rg An	x ² .5	±	4-H	4-H	3-H	표	H.E	H.E	4-SMe	4-SEt	3-H	3-Н	3-0Bn	4-H	4-NHBn	3.H	positions positions			
		- N- 8	x1.5	2.H	2.H	2.H	F.	2.H	7. 1.	7-F	Z.H	7.	2-H	2-H	7.H	H-2	7.F	2.H				
		4 4	R13.1 X1.2	82	I	Ξ	Ξ	x	r	Ŧ	Ξ	Ξ	I	I	Ξ	I	Ŧ	Ξ	tutio			
40		× × × × × × × × × × × × × × × × × × ×	R ₁₂ *1	S.H	H.S.	H.S.	5-SMe	5-SEI	5-S ⁿ Bu	H-S	H.S.	H-S	5-H	H-S	5-Me	5.E(S-OMe	S-OEI	substitution substitution	ď		2
		× ZEX	R ₁₁ .1	4-0Me	4-OEt	4-OnPr	Ŧ	4.H	H.	3-F	ာ့င	3-84	3-NH2	3-NHMe	H-C	3.H	Ŧ.	# +			CH2)u-	
45		R1 X 1 X 1 X 1 X 1 X 1 X 1 X 1 X 1 X 1 X	Sastitution Regi.	6	3	6	၉	ဂ	P	4	4	4	4	*	4	4	6	6	*1:Numerals represent	. R3) E	Œ
		СН2)л-	-	z	z	z	z	z	z	z	z	z	z	z	0-2	0-8	0 2	0-N (9)	rals		-(CH ₂)	
50		Ž .	a	9	(9)	9	9	9	(9)	9	9	9	9	(9)	9	9	9		1 1 1 1		# ≩	
		£ &	컦훅	391	392	393	394	395	396	397	398	399	60	4 0	405	403	404	405	*1:N	I	*	

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S B B	P3	Ŧ	Ŧ	¥	I	Me	I	I	н	H	¥	I	н	Ι	x	Ξ
E	ء	٥	°	-	0	0	0	-	0	0	0	0	0	0	0	٥
S A.	22	CO2tBu	CO2tBu	x	¥	н	CO ₂ tBu	x	CO2tBu	CO2tBu	I	I	CO2lBu	CO2¹Bu	CO2lBu	CO2¹Bu
© B - 2	Æ	CO2tBu	CO2lBu	CO2tBu	CO2tBu	CO21Bu	ဂရာဇဝ၁	CO ₂ tBu	CO2 ¹ Bu	CO ₂ tBu	CO2tBu	CO2tBu	CO2¹Bu	CO21Bu	CO ₂ tBu	co ₂ ¹Bu co ₂ ¹Bu
5 4 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	Substitution . position of Wa-	8	٣	4	£	6	3	2	3	3	3	3	3	8	£	3
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4 Rg Rg (4)	x3.5	9-H	9-H	5-H	H-9	5-H	5-Me	5-H	5-H	5-H	5-Н	5-H	9-H	9-H	H-5	5-н
P8 P7 3 W	z. ² x	H-7	4-pyrrolidin-1-yl	3-Н	4-H	H-4	H-7	4-H	4-H	4-CI	4-M8	4-F	4-H	4-H	4-H	4-OMe
# \$ 7 - E	z.¹x	2-Me	2-H	2-H	2-H	2.H	2-H	3-Н	2-OMe	2-H	2-Н	2-H	2-0Et	2-H	2-H	2-H
-4 e [£]	.e ₈	6-OMe	6-0Me	6-OMe	6-OMe	6-OMe	6-OMe	6-OMe	6-OMe 2-OMe	6-OMe	6-OMe	6-OMe	6-OMe	6-Me	6-OMe	8-OMe
7 HB	Rg*1	5-н	5-H	5-H	5-H	5-H	9-H	5-H	9-H	5-H	9-H	5.H	5-H	5-H	5-H	5-H
4 2 H	R7.1	4-H	4-H	4.H	4-H	H-4	H-4	4-H	4-H	4·H	4-H	H-4	4-H	4-H	4-H	4-H
ج ہے	Substitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
× Şŧž×	R ₆ .	NO ₂	NO2	200	NO2	NO2	NO ₂	NO2	NO2	NO ₂	NO2	NO2	NO2	NO2	NO2	NO ₂
C +3	2	N	Z	z	z	z	z	Z	z	z	z	z	z	СН	СН	용
g-0- g Σ) - 2 =	٨	CR6	CR_6	CRe	CR6	CR6	c_{R_6}	СЯв	CR6	CR6	СР6	CR6	СЯ6	СЯВ	CR6	(2) CR ₆ CH
G ₩3	٨	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)
R1 X1 X2 R2 - (CH2)m-t - (CH2)m-t 1 R2	Er. No.	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420
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*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

R3

*:W = -(CH2)m - -(CH2)m - R1

R4

R2

			R ₅	I	I	I	I	Ξ	I	Ŧ	I	Ξ	Ξ	Ξ	I	Ξ	I	I				
5			E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
•		R 8	2	Ŧ	Ŧ	Ξ	x	I	Ξ	Ξ	I	S.	Ξ	Ξ	Ξ	H	н	H				
		E TAN	F3	×	Ξ	I	I	Ξ	I	I	I	ŝ	ŭ	Ξ	Ξ	I	н	н				
10		7-	=	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0	yed.			
		-/ s 8 4 ·	R2	CO2tBu	CO218u	Ξ	Ξ	CO2tBu	CO2tBu	I	I	I	I	CO2¹Bu	I	н	н	H	employed			
15		2 2 2	B.	CO21Bu	CO2tBu	mg ₂ COS	CO2 ¹ Bu	CO2IBu	CO2tBu	78 ₁ CO2	CO21Bu	CO218u	CO2tBu	CO21Bu	CO21Bu	cO ₂ tBu	CO2lBu	CO2¹Bu	(2)-(2)			
20		8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Substitution	e	6	ы	г	c	က	67	n	6	6	6	3	3	2	3	of			
		A 2	X4.5	H.	H-9	H.º	H-9	H-0	Н-9	H-9	H-9	H-9	H-9	Н-9	Н-9	Н-9	н-9	Н-9	structural formulas benzene ring.	<u>,</u>		
		R S R R R R R R R R R R R R R R R R R R	x3.5	5.H	5-H	F.S	5-H	5-H	5-H	팏	5-H	H.S	7.H	F-F	Р-9	5-H	5-Н	5-H	ural e rin			
25	59	1	X2.2	#. 4	H.	H.	H-4	H-4	4-H	Ŧ.	H-4	Ŧ	4-H	H-4	4-Et	4-OEI	4-H	4-H	structural for			
	Table	Rg A≊	2,1x	2-H	#.Z	2-H	2-H	7.H	2-H	2.H	2-H	2-H	2-H	2-Me	2-H	2-H	3-н	2-Cl	the st			
30	Tal	- E	Rg.1	6-OM6	6-OMe	H-9	H-9	ij G	6-01/48	H.9	H.	H-9	H-9	H-8	6-н	Н-9	Н-9	₩-9	# 8			
		9 A 2 3	R8.1	5-NO ₂	F.	H.S.	5-H	Ŧ.	F.S	S-OMe	Ŧ	F.S.	5-Н	Ŧ	5-н	Н∙\$	9-Н	Н-6	positions positions			
35		(2) - (2)	R ₇ .1	H.4	. H-4	4-CO2Me	4-Me	4-H	4-H	4-H	H-4	4-Me	4-Me	4-M8	4-Me	4-Me	4-Me	4-MB				
40		A A	Smitter of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	substitution substitution	A ₁	19.	3
		× × × × × × × × × × × × × × × × × × ×	a.	I	ZON	н	٠	NO2	CF3	NO2	δ	r	I	I	π	I	I	н	(`	ν - υ(i	
45		CH2)m1	Z	z	Z	Z	z	z	z	СН	СМе	z	z	z	z	z	z	Z	represent represent	£-3	(<u>2</u> (<u>2</u>	4
		X-(CH2)-C-(CH2)-X-X-X-X-X-X-X-X-X-X-X-X-X-X-X-X-X-X-X	٨	CR6	СЯв	СРв	СВв	СЯв	СРв	CR ₆	CR6	CR6	CR6	CR6	CRe	CR6	CR6	c_{R_6}			ار قر	Ľ
		(CH ₂)	٧	(2)	(2)	(3)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	eral		Į Į	
50		Z Z	고 호	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	*1:Numerals *2:Numerals	;	*: W = -(CH2)m-	

			R ₅	Τ_	Ī_	Γ_	Γ_	_	Ι_	Γ_	_	<u> </u>	Γ_	Ė	Ė	Γ_		<u>; </u>	ı			
			-	I	Ξ_	Ξ	I	I	Ξ	Ŧ	Ξ	I	I	Ξ	Ξ	Ξ	II.	I				
5			E	0	٥	0	0	0	0	0	٥	0	٥	ò	0	0	۰	0				
J			8	-CH2CH2CH2	Ξ	Ξ	Ξ	Ξ	I	I	I	Ξ	I	I	Ξ	I	I	I				
		a R	સ	CH2CI	Ŧ	Ξ	I	Ξ	I	I	Ŧ	Ŧ	I	I	I	Ŧ	I	I	 - -			
10		à-1€ €	c	0	-	0	0	0	0	0	•	0	0	0	0	0	0	0				
		A 24	8,	I	I	നു≷ഗാ	™9,200	CO ₂ tBu	I	I	r	I	I	CO ₂ (Bu	CO ₂ tBu	Ŧ	I	r	employed			
15		# S = # @	F.	CO ₂ tB _{LU}	_{CO2} 18 _U	നമുഗോ	2O2	ngZo3	CO2 ^{tBu}	™BrZO2	ma ₂ COS	CO2 ^{1Bu}	CO2fBu	ငတ္ဥရော	CO ₂ tBu	CO2 ^{tBu}	CO2 ^{tBu}	CO21BU				
20		2 A B A 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Substitution position of Be	6	4	3	6	9	9	e	3	3	6	6	3	6	6	က	s of (2)-(7)			
		£	× .5	H-9	Н-9	Н-9	H-9	H-9	н-9	H-9	Н-9	Н-9	H-9	Н-9	Р-Я	Н-9	H-9	H-9	mula			
		န် _မ န	x3.5	9-H	Н-9	Н-9	5-H	9-H	9-н	5.H	5-H	H-6	5.H	5-H	5-H	5-H	5.H	5-H	for tng.			
25	0	3 2 - 3	x2.2	4.H	3-н	H-4	4-C	H-4	4-H	±	4-H	4·H	4-H	4-H	4-H	4-H	H-4	4.H	tura ne r			
	.е 30	4	x,2	7÷	2-H	2-OEt	2-H	2-H	2-н	7.H-2	2-H	4-2	2-H	2-H	2-H	2.H	2.H	2-H	structural formulas benzene ring.			
30	Table	A. A. A. A. A. A. A. A. A. A. A. A. A. A	Rg.1	H-9	H-9	H-9	н-9	6-OMe	Н-9	6-OMe	6-OMe	6-OMe	6-OMe	6-CH(CO2M8)2	6-CMe(CO ₂ Et) ₂	6-SMe	H-9	6-Мө	in the			
35			B.	5.H	5-H	5-H	5.H	H-S	S-H	1-S	5-H	9-H	H-8	H-6	5-H	H-6	₽-ç	5-H	siti			
		2 2 6 H9	R ₇ .1	4-Me	4-Me	4-Me	4-Me	4-H	4-H	++	4-CO2H	4-CH ₂ OH	4-Me	4-H	Ť.	4-H	4-Me	4-Me	tion po	,		
40		^x-a, 4	Substitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	substitution positions substitution positions	Ę	R ₂	ı
		××××××××××××××××××××××××××××××××××××××	P _e	I	I	I	H	CN	เว	емгоэ	I	н	I	NO ₂	NO ₂	NO2	Ξ	I	represent s		72)n - 12 	
45		CH2).	7	z	z	z	z	z	z	Z	z	z	N	z	z	z	z	Z	pre	£-	<u>,</u>	ġ.
		R-0-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-	۲	CR ₆	S _B	CRe	CR ₆	СР6	CR6	СЯв	СЯв	CR ₆	СР6	CR_6	СЯв	CR ₆	CA ₆	CR6	ls re		ئ آ	•
		(CH2)	V	8	<u>@</u>	2	2	(2)	<u>2</u>	(2)	②	(2)	(2)	(2)	(2)	(2)	(2)	(2)	era		<u>ф</u>	
50		R3 X1 X2 R2 N-(CH2)n-(-(CH2)m-1 X4 X4 6 R2 X4 X3 X4 (1)	Ex. No.	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	*1:Numerals *2:Numerals		*: W = -(CH2)m-C(CH2)n	

			salt							Ž.	Σ E	2HCI	HC	НС	HC	HCI	ÖH	НСІ			
5			æ	I	I	I	Ξ	I	I	I	H	I	Ξ	н	н	I	I	Ξ			
			ε	0	٥	0	0	0	٥	0	0	0	0	0	0	0	0	0			
		R 8	2	н	I	I	I	I	I	I	Ξ	I	I	I	Me	H	I	π			
10		E E	R ₃	I	н	I	I	I	I	I	I	I	Ι	н	Me	I	Ι	Ι	ĺ		
		3	و	0	0	٥	0	٥	0	0	0	0	ı	0	0	0	1	0	ed.		
		88	R2	I	I	I	I	Ξ	I	I	H	I	н	н	н	н	I	I	employed		
15		E- 12 2 8 6	R ₁	ಗಕ್ಕಿ೭೦೦	ಗಿಕ್ಕಾರಿಂ	ಗಿಕ್ಕಾರಿಂ	ငတ္ခႏြစ	CO2¹Bu	ငတ္ဒႏβာ	I	I	I	I	H	I	I	н	H	(2)-(7) en		
20		**************************************	Substitution position of W	3	3	3	6	၉	6	8	၉	6	4	3	ဧ	ဗ	2	3	of		
		2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -	x4.5	Н-9	Н-9	H-9	H-9	H-9	H-9	H-9	H-9	H-9	H-9	6-OMe	H-9	Н-9	Н-9	Н-9	cmula		
<i>25</i>		8 1 5 8 B 1 8 A A	x3.5	9-H	5-H	5-H	F.F	5-H	5-H	5-H	5-H	5.H	H-9	9-H	S-H	5-Me	5-н	5-H	il fo		
	Table 31	39 A= 3/W A	x ₂ .2	4-H	4-H	4-H	£.	4.H	±4	H-4	Ŧ.	4-pyrrolidin-1-yl	H.E	4-H	H-4	4-H	H-4	H-4	e structural formulas e benzene ring.		
30	Ţ	(5) - (5)	z.1x	2-H	₽ . 5	2.H	2.H	H-%	₩.	2.H	2-Me	2.H	2-H	2-H	₽.	2-H	H.E	2-OMe	in the		
		4 5 13 2	P. g.	н-9	6-OM6	6-OM6	6-OMe	9МО-9	6-OMe	6-OMe	6-OMe	6-OMe	6-OMe	6-OMB	6-0Me	6-0Me	6-OMe	6-OMe	positions positions		
35		7 HB 7 S H9 (2)	R8-1	5-н	Я-9	F.F.	5.H	4.5 H-5	5.H	5-NO2	H.	F.S	5.H	H-6	F.	5-H	5-H	5-H			
		\$\f\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	R7.1	4-Et	4-H	I-1	¥.	4-H	4.H	4 ±	H-4	H-4	# +	4-H	4-H	4-H	4-H	4-H	tion		
40		2	Substitution position of A	2	2	2	2	8	8	8	~	~	8	8	8	8	8	8	substitution substitution	č	-
-		V. 4 €×			СО2Н	CONH2	сн ₂ он	Me	CHO	Ξ	ZON	ğ	Ş	Š	2 V V O ₂	SQ2	NO ₂	№			CH ₂)n-N
45		ε 1 ξ	2	z	z	z	z	z	z	z	z	z	z	z	z	z	z	z	epre	£-	- ۲
		2) R-C-B	Y	(2) CR ₆	CR6	CRe	CR ₆	C.Be	S,	9 8	9 8	S _B	S B B	S, B	8	CR6	S. S.	CRG	ls r		CH2)m
50		5	۷ .	(2)	(2)	(2)	(2)	(2)	8	8	8	8	(2)	(2)	2	(2)	(2)	(2)	mera		7
		R. R.	겳	453	452	453	454	455	456	457	458	459	460	461	462	463	464	465	*1:Numerals represent	. eE-	₹

				salt	를	豆	亨	호	호	ᅙ	2HCI	2HCI	2HCI	2HCI	HCI	ΗĊ	2HCI	2HCI	2HCI				
5		د 8 8		R ₅	Ī	I	I	Ī	Ī	I	7 H	7 H	H 2	H 2	Н	H	Н 2	H 2	Н 2				
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		A= 2		2	I	Ī	Ī	I	I	I	I	I	ī	I	I	н	H	Me	I	yed			
10		5 88 S		F3	Ī	Ī	Ξ	Ξ	Ī	I	I	I	I	I	H	н	н	Me	E E	employed			
		e-1-2-	Р ₉	c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-(7)			
15		A 2 - 2		R2	I	Ξ	Ī	I	Ξ	Ξ	I	I	Ξ	I	H	I	I	Ξ	I	(2)-(
		8		R ₁	Ξ	Ξ	Ξ	Ξ	Ξ	Ξ	Ξ	I	Ξ	Ξ	I	I	I	Ξ	H	of (
20		4	R ₉	Substitution position of We	င	င	၉	6	င	9	3	6	8	3	3	3	3	6	8	formulas ng.			
		8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9		X4.5	H-9	Н-9	H-9	H-9	H-9	H-9	6-Н	Н-9	H-9	Р-9	н-9	н-9	Н-9	Н-9	Н-9				
25	32		- €	z. [£] X	9-H	9-н	S-H	5.H	5-H	5.H	9-H	5-H	9-H	5-H	9-Н	5-Н	Н-8	5.H	H-6	structural benzene ri			
		*		x ² .5	<u>4</u>	4-F	₽÷	±	4-H	4.H	4-H	4-H	4-H	4-H	4-H	4-H	4-H	Ŧ.	4-H				
	Table	\$\f\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		x1.5	2-H	2-H	2-0EI	2-Cl	2-H	2·H	2-H	2-H	2-H	2-H	2-Н	2-н	2-Н	2-H	2-H	the			
30	Ħ	87 88 87 88 3 2	(3)	R ₉ .1	6-OMe	6-OM8	6-OMe	6-OMe	6-OMe	6-OMe	6-OMe	6-OMe	H-8	е-ОМе	Р-9	Н-9	Н-9	H-9	H-9	ns in			
		F 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8		R8.1	5-H	5-H	5.H	5-H	5.H	5.H	S-H	9.H	9-H	9-H	5-OMe	5.H	8-H	5-H	F.F	positions positions			
35				R7.1	4-H	4-H	4-H	4.H	4-СО2Мв	4-CO ₂ H	4-СН2ОН	4-Me	4-Me	4-H	4-H	4-H	4-Me	4-M8	4-Me				
40		**************************************	- R _S	Substitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	substitution substitution	F,		Ä ₂
		××+××	?	8	NO2	NO2	NO2	NO2	н	I	н	I		CF3	20N	NO2	I	I	I			12)n-N	
45		CH ₂)π	_	7	z	z	z	z	Z	z	z	z	z	z	СН	СМв	z	z	z	represent represent	- A3	<u></u>	.
		&__\ 4	٦	Ý	CR_6	CR6	CR6	CR6	CR_{6}	СРВ	CR6	CR6	z	CR_6	CR6	СR ₆	CR6	CR6	CR ₆		_	12)m (2	
50		(CH2)		4	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	eral		5	
		X X X X X X X X X X X X X X X X X X X		Ex. No.	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	*1:Numerals *2:Numerals		*: W = -(CH2)m-c-(CH2)n-	ť

			salt	2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	2HC1	2HCI	2HCI	2HC	2HCI:	ᅙ	Ž.	Ş	2HCI				
5			R _s	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I				
		E 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	ε	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
10		E STE	2	Ξ	Ŧ	I	I	Ξ	Ξ	Ξ	2CH2-	I	Ŧ	x	×	I	I	I	Ġ.			
		8a ♣	æ	Ξ	I	I	I	Ξ	I	Ξ	-СН2СН2СН2	I	I	I	Ŧ	I	I	Ŧ	employed			
		F- 1 2 2 6	ح	0	0	0	-	0	0	0	0	-	0	0	0	0	0	0				
15		6	8	Ξ	Ξ	Ξ	Ξ	I	I	I	I	I	I	I	I	I	H	I	(2) - (7)			
		85 A	Æ	Ξ	Ξ	I	I	I	I	X	I	н	Ŧ	I	x	I	н	I	of (2			
20			Substitution position of P	c	3	9	2	3	3	3	3	4	6	ေ	၈	က	9	6	structural formulas o			
		8 2 2 2 2 4 8 8 8 8 8 8 8 8 8 8 8 8 8 8	X .2	H-9	H-9	H-9	H.	H-0	H-9	H-9	H-9	H-9	H.	H-0	H-9	H-9	H-0	H-9	al fo			
25	33	\$ - \(\alpha \)	x3.5	5. H-3	H-3	5.H	H-S	H-6	5.H	5-H	9.H	5.H	9-H	H-6	9-H	5.H	5·H	5-H	structural f) 		
	Table	₽	X2.2	4-H	4-E	4-0Et	#.4 H.4	Ŧ.	H-4	H-4	4·H	3-H	4-H	5	4-H	H-4	H-4	# .				
30	Tal	3 - E	x1.2	2-Me	2.H	2·H	3.H	2.CI	2.H	2·H	2·H	2.H	20Et	2·H	2.H	2·H	2.H	N.H.	in the			
		# #¥2,	F. 64	H-9	H-9	#-9	Н-9	H-0	6-Me	Н-9	Н-9	H-9	H-9	H-9	6-OMe	H-9	6-OMe	6-OMe	i suo) }		
35		ھ ا ہ م	Re-i	5-H	5-H	S-H	Н-9	9-H	H.	9-H	H-S	5-H	5.H	5-H	5-H	5.H	5-H	5-H	positions	! ; !		
		- 22	R ₇ .1	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-EI	4-Me	4-Me	4-M9	4-K	±.	H-4	H.4	# .	og uo			
40		A S	Substitution position of A	2	2	2	2	8	2	2	2	2	2	2	2	2	2	2	substitution substitution	-	-	7
		01 10 = \4_		I	I	I	Ξ	I	I	Ξ	Ξ	I	Ξ	Ξ	S	ರ	CONH2	We			¥	E,
45		CH2)31	2	z	Z	z	z	z	z	z	z	z	z	z	z	z	z	z	represent	ت	Į.	- A
		&	٨	CR ₆	CR6	CR6	CR6	CR ₆	СЯ6	S. B.	CR ₆	CR6	CR6	CR6	CR6	CR6	CR6	CRe	s rep	. u	12)m-C	Œ
		-(СН2)	٧	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(%)	eral	: ! !	S	
50		R2 X-1CH2)n-C-(CH2)m-1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X-1 X	Er. Ro.	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	*1:Numerals		* : W = -(CH2)m-¢(CH2)n-	•

			salt	Š					2HC!	SHC	2HCI	2HCi		2HCI	salt					 			
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10		ŧ"	-	0	0	0	0	0	0	0	0	0	0	0	u	0	0	0	0	employed			
		* J. S.	22	Ξ	™ 200	Ξ	ကရူငီဝ၁	I	I	I	Ξ	I	င်လူမျာ	Ŧ	R2	I	н	н	н	(7) em			
15		E-12-8	@	ī	CO2Bu C	CO2 ^t Bu	0 mg,200	CO2 ^{tBu}	ェ	I	I	I	၁ ကရူဇီဝ၁	I	A,	CO2tBu	н	CO ₂ tBu	Ξ	(2) - (.			
		88 4	-	-	8	8	8	8	_	_	_	<u> </u>	8			8	_	၁		οĘ			
20		£ 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	(5) Substitution position of	9	e	3	ဗ	m	က	m	6	ю	ю .	3	Substitution position of	3	3	3	9	structural formulas benzene ring.			
		* ₹	×4.5	H.	H-9	6-H	H-9	H-9	H-9	H-6	H-9	H.	H-9	Н-9	X4.2	Н-9	н.9	Н-9	Н-9	1 for	1		
05		2 × 4 ×	x3.5	H.S.	풄	5-н	5-H	5-H	5-H	H-S	5.H	5-H	5-H	5.H	x3,2	P-9	P-6	5-H	5-H	tura ne r			
25	34	3 - 5						<u>1.</u>				14-1-				_				ruc			
	Table	8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	x2.5	4-OMe	# .	4. H-4	4-OMe	4-pyrazol-1-yl	Ŧ	4. H.	4-OMe	4-pyrazol-1-yl	±.	±4	X2.2	4-H	4-4	¥	H.4	the st			
30	Ţ	E 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	<u>د</u> '۲	2-H	2-H	2-H	2-H	2-H	2.H	2-H	2-H	2.H	2-Onpr	2-OnPr	×1.5	H-2	2-H	4-5	7.H	nt st			
		60 - ₹		8-OMe	H-9	H-9	H-9	H-9	H-9	H-9	H-9	6-H	н-9	H-9	F. 64	•				positions positions	 		
35		Ra S P P P P P P P P P P P P P P P P P P P	R8-1	5.H	5-Me	5.H	S-H	F.	S-Me	5.H	5-H	F.H	9-H	5.H	R8.1	5-Me	5-Me	5-H	H-S	,			
		**************************************	R7.1	H-4	H-4	H.4	4-Me	4-Me	H.4	H-4	4-M9	4-M8	4-Me	4-Me	R7.1	±.	H-4	4.Me	4-M6	utto			
40		×	citution ties of A	2	2	2	8	2	2	2	2	2	2		Substitution position of A	2	~	2	2	substitution substitution	ě	'~	4 2
		× ŽĮŽ×	8	Š	Ξ	Me	Ξ	Ξ	I	₩	Ξ	Ξ	Ξ	Ξ	A N	•				sent		.H2)n-	
45		CH2)a	2	H U	z	z	z	z	z	z	z	z	z	z	2	•				represent represent	£.	- \$-	. 4
		&_Ó− ₽	>	CR6	ဗို	မှ	S B G	S. B.	S. Re	CR ₆	CR ₆	C _R e	S. Be	S S	-	s	s	s	s			45)m-	
		(CH2)	4	8	8	8	8	8	8	8	2	<u>2</u>	8	2	⋖	(3)	ε	ε	ε	era		\$	
50		N. V-(CH2)J-(-(CH2)J-(-)	F	496	487	498	489	200	501	505	503	504	505	909	Ex. No.	507	508	509	510	*1:Numerals *2:Numerals		*: W = -(CH2)m-¢-(CH2)n-	

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5		89	salt					CF3CO2H	CF3CO2H	СҒ3СО2Н	СЕЗСО2Н	salt			2HCI	2HCI							
		E - E	P _S	Ξ	Ξ	I	Ξ	I	Ξ	I	Ξ	RS	Ξ	Ξ	I	Ξ	Ξ	I	Η	<u></u>			
		- F- C	ε	0	0	0	0	0	0	0	0	Ε	0	0	0	0	0	0	0	уес			
10		Ą	æ	Ξ	Ξ	I	Ξ	Ξ	Ξ	I	Ξ	2	I	Ξ	H	Ξ	Ξ	н	Ξ	employed			
		4/2 88	&	Ξ	Ξ	I	Ξ	Ξ	Ξ	Ξ	Ξ	જ	Ŧ	I	Ξ	Ξ	Ξ	Ξ	I				
		2-29	ء اھ	0	0	0	0	0	0	0	0	ے	0	0	0	0	0	0	0	(2)-(1)			
15		* * * * * * * * * * * * * * * * * * *	82	CO2∰	CO2¹Bu	നമുഗാ	CO2 ^{tBu}	I	I	н	H	R2	Н	H	н	н	I	I	н	of (2			
		E-1-7-2:	(5) R ₁	CO ₂ tB _W	CO2 ^{tBu}	ഷൂരാ	202 18m	Ŧ	Ξ	I	Ξ	R ₁	നമുമോ	ငတ္ခါမျာ	Ξ	н	I	н	H	formulas q.	•		
20		F8 3 4 2 4	Substitution position of We		0	6	6	က	6	က	6	Substitution position of Pt	9	3	3	3	3	6	6	ב			
25	35	2 - S	X4.2	H-9	H-9	H-9	H-9	H-9	H-0	H-0	H-9	X4.2	Н-9	H-9	Н-9	Н-9	н-9	Н-9	Н-9	structural benzene ri			
		9 A=	x3.2	S.H	S.	5-H	S-H	5.H	Σ. Τ	F.	S.H	x3,2	5-H	Ŧ.	S.H	F.F.	5-H	5-H	5-H	the s			
30	Table	R 2 - 6	×2.5	# 7	# .	4-H	4-OMe	H-4	# .	Ŧ	4-0M8	x2.5	<u>5</u>	4-Me	<u>5</u>	4-M9	4-H	4-H	4-H	5 5			
	-	# # * ·	x1.2	2·H	2-0Et	2-M8	2.H	2·H	2-0Et	2-M8	2-H	x1.2	2-OEI	2-0Et	2-OEt	2-0Et	2-H	2-H	2-H	positions positions	 		
		8 5 8 8 8 8	1-	<u> </u>		·	·	·				P ₉ .1	H-9	F.H.	Н-9	H-9	H-9	6-M ₈	H-9	osi	!		
35		- 8	. g	5-Me	5-Me	5-Me	5-MB	5-Me	S-Me	5-M8	5-Me	R8.1	5-H	5-H	5.H	9-H	5-NO2	5-H	9-H				
		- 4 €	R7.1	4-H	4.H	4-H	4-H	4-H	4-H	4-H	4-H	R7.1	4-Me	4-Me	4-Me	4-Me	4-H	4-Me	4-CN	itut			
40		× - × = ×	Substitution position of A	2	2	2	2	2	2	2	2	Substitution position of A	2	2	2	2	2	2	2	t substitution t substitution		Ƴ	4 2
		× \$ 1 × ×	A ₆	·	·	٠	٠	٠	,	·	·	æ	I	I	I	Ξ	ζ Q	Z O	I	represent represent		CH2)u.	
45		(CH ₂)	7	·	·	·	·	·	·	·	ŀ	2	z	z	z	z	z	z	z	repr	. چ.	Ϋ́-	₽.
		E-0-E	-	0	0	0	0	0	0	0	0	>	CR ₆	S,	S. Re	CR6	A B	9 8	કુ			H2)m-	
		4 5)	⋖	ε	ε	ω	ε	ω	ε	ε	ε	4	(2)	(2)	(2)	8	(2)	8	(2)	mera	! !	2)	
50		R3 4 2 4 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	편 호	511	512	513	514	515	516	517	518	면 면	519	920	521	522	523	524	525	*1:Numerals	<u> </u>	*: W = -(CH2)m-c-(CH2)r	
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			ЯS	I	I	I	I	I	Ι	Ξ	I	I	I	Ė	Ŧ	I	I	I	
5			E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		F.	\$	Н	I	I	I	н	H	I	I	I	I	I	I	I	I	Ι	
		E	Яз	н	H	I	н	н	н	н	H	I	Ξ	I	I	Ξ	I	н	· pa
10		Ą	۲	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	employed
		5 - 8 0 8 2 - 8 0	R2	н	н	H	н	I	н	н	н	н	Ξ	I	I	н	н	CO218u CO218u	
15		A 2	A,	I	I	I	I	I	I	I	I	x	Ξ	≖	÷	I	I	CO2 ^{tBu}	(2) – (1)
20		E 8 6	Substitution position of Pe	3	ε	3	ε	9	3	ε	ε	ε	ε.	3	3	3	3	C	formulas of ng.
		₹ 	X4°2	H-9	6-н	Р-9	Н-9	H-9	Н-9	Н-9	Н-9	Н-9	Н-9	н-9	Н-9	H-9	P.	4.9 H-0	ing.
		8 × 5 - 3	x3.5	5-H	5-H	5-H	5-H	5.H	5-H	5.H	5-H	5-H	5-H	5-H	5-H	5-H	5.H	5.H	structural for benzene ring
25	36	E	x2.5	H-4	4-H	H-4	4-H	Ŧ	H-4	4-H	H-4	H-4	4-H	4-H	H-4	4-H	4.H	H-4	truc
		ة 15 6 Rg A=	x1.5	2-H	2.H	2-H	2-H	2.H	2-H	2.H	2.H	2.H	2.H	2-H	2-H	2-H	2.H	2-OMe	the s
<i>30</i>	Table	3-6	Pg.1	H.	6-Me	н-9	H-9	H.9	6-Me	H202-9	6-Me	구.	6-OMe	H.	H.	H-9	6-Me	H-9	r o
		A 8 A	P8.	S CN	H.S.	5-H	5-CO2H	5-CO2H	H-S	5.H	H-S	ς Ω	F. H.	H-S	5-Br	5-CI	H-S	F.F.	positions positions
35		2 - E	R7.1	H.4	4-CO ₂ Et	4-CO2H	H-4	H-4	4-CO2H	H-4	H-4	# .	4-CONH2	±	4-H	4-H	4-H	4-Me	i e
40		H3 X1 X2 H3 V-(CH2)m-1-(-(CH2)m-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1	Substitution position of A	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	substitution substitution R1 R2
		× \$ 1 × × × × × × × × × × × × × × × × ×	Re	I	S	I	Ξ	ច	Ξ	Ξ	CONH2	CONH2	r	CONH2	I	៊	I	I	*1:Numerals represent *2:Numerals represent R3 *:W = -(CH2)m - C-(CH2)n - N
45		3 (CH ₂	7	z	z	z	z	z	z	z	z	z	z	z	z	z	z	z	repr R-C-3
		α- ύ- α	>	CRe	CRe	S. B.	CRe	CR ₆	SRS	S _B	S _B	S ₈	CRe	CR6	CRe	S _B	S _R		als als CH2)m
50		, Č	4	2	(2)	(2)	8	8	2	8	8	2	(2)	2	(2)	8	(3)	(2)	mer.
30		E E	결	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	*1:N *2:NI *: W

			salt	2 KC		2HCI		2HCI		2HCI	2HCI	2HCI	2HCI	2HCI	2HCI	SHCI;	2HCI	2HCI	
5			P _S	I	I	Ξ	I	Ξ.	I	I	I	I	н	н	н	H	Н	H	
			E	•	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		£ £ £	æ	Ξ	I	I	Ξ	I	I	x .	I	Ξ	H	I	H	H	×	I	
10		3-(1)	£	I	I	Ξ	Ξ	Ξ	I	X	I	Ξ	Ξ	I	I	I	Ξ	I	•
		* &	C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	oyed
15		2 S 8 8 8	82	I	rg ₂ cos	Ŧ	Ξ	н	н	ĸ	н	I	н	н	н	н	I	н	employed
		4 ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° ° °	F.	x	CO ₂ tBu	I	CO ₂ tBu	H	CO2 ^{tBu}	I	I	H	I	Ξ	I	Ξ	Ξ	Ι	(2) - (2)
20		E 4 2 2 2	Substitution position of FF	3	က	င	က	3	E	ဗ	3	3	3	3	3	3	3	3	structural formulas of benzene ring.
		£ 3,	X4.2	H-9	9-H	H-0	Н-9	н-9	н-9	Н-9	н-9	6H	н-9	Н-9	H-9	Н-9	Н-9	Н-9	form
25		8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	x3.5	5-H	5.H	5-H	5-H	5-H	5-H	У- Н	9-Н	5-H	9-Н	5-H	5-H	5-Н	5-Н	5-H	ural e ril
	37	\$ - \$ \$	×2.2	4-H	H-4	4-H	Ŧ.	4-H	4-H	4-H	4-H	4-H	4-H	4.H	4-Me	4-Me	4-Me	4-Me	ruct
30	Table	2 4 5 8 4 5 10 10 10 10 10 10 10 10 10 10 10 10 10	x1.5	2-OMe	2-OlPr	2-OlPr	2-O ^r Bu	2-OnBu	2-OfBu	2-O ^(B) U	2-OCH2Ph	2-ОСН2СН2Рһ	2-EI	2-CH ₂ Ph	2-OMe	2-OiPr	2-O ⁿ Bu	2-OfBu	in the
05		∢	F. 64	Н-9	H-9	H-9	H-9	Н-9	Н-9	H-9	F-6	H-0	Н-9	Н-9	Н-9	H-0	H-9	મું 9	positions positions
35		2 2 2 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	R8-1	H-9	5-H	꾸	H-S	Н-5	H-S	H-S	H-S	5-H	H-S	H-6	H-S	H-S	H-S	A-R	
		**************************************	, R7.1	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	4-Me	tution
40		%% <u>-</u> {	Smstitution position of A	2	2	2	2	2	2	2	2	2	2	_ 5	2	2	2	2	substitution substitution R1
		x\$ + \$x	8	Ξ	I	I	I	I	H	н	Τ	Ξ	H	н	I	Ŧ	I	Ξ	sent sent H2)n-
45		(CH2)	2		_	z	z	z	z	z	z	z	z	z	z	z	z	z	Pre:
		E-0-E	٨	CR ₆	CR6	CR6	CR ₆	CR6	CR6	CR6	CR6	CR6	CR6	CR6	CR6	CR6	CR6	CRe	1s r. 1s r. H ₂)m-
50		(C F 2)	٧	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	mera mera
		RA V-(CH2)n-C-(CH2)m-1 A X4 K6 6 1 A X4 X4 6 1 A X4 X4 6 1 A X4 X4 X4 X4 X4 X4 X4 X4 X4 X4 X4 X4 X4	Er. No	541	542	543	544	545	546	547	548	549	250	551	552	553	554	555	*1:Numerals represent *2:Numerals represent R3 *:W = -(CH2)mC-(CH2)n-I

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Example 1

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Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-3-nitropyridine

[0055] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (1.50 g), triethylamine (2.0 ml), 2-chloro-3-nitropyridine (1.10 g) and anhydrous dimethylformamide (15 ml) was stirred at 60°C for 20 h and, thereafter, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 3:1) to give 1.42 g of the titled compound (yield, 69%).

 1 H-NMR(CDCL₃) δ:1.47(18H, s), 4.81(2H, s), 6.83(1H, dd, J=8.3, 4.3Hz), 7.11(1H, d, J=7.9Hz), 7.34(1H, dd, J=7.9, 7.9Hz), 7.55-7.63 (2H, m), 8.47(1H, dd, J=4.3, 1.7Hz), 8.53(1H, dd, J=8.3, 1.7Hz), 10.11(1H, brs)

15 [0056] The procedure of Example 1 was repeated using corresponding aniline derivatives or corresponding halogenated derivatives to give the compounds shown in Tables 38 - 43 (under "Reaction condition" in the tables, base:(1) is triethylamine and base:(2) is diisopropylethylamine).

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Spectral data	¹ II-NWR (CDC1 ₂) & 1. 47 (18H, s), 4. 80 (2H, s), 6. 77 (1H, d, J=9. 2Hz), 7. 16 (1H, d, J=7. 3Hz), 7. 26-7. 39 (3H, m), 8. 23 (1H, dd, J=9. 2, 2. 6Hz), 9. 08 (1H, d, J=2. 6Hz)	'H-NNR (CDC1,) & 1. 46 (1811, s), 2. 57 (311, s), 4. 79 (211, s), 6. 66 (114, d, 1=5. 0Hz), 7. 06 (114, d, 1=7. 6Hz), 7. 26-7. 33 (114, dd, 1=7. 6, 7. 6Hz), 7. 46 (114, s), 8. 18 (114, dd, 1=5. 0Hz), 9. 14 (114, brs)	'H-NMR(CDCI ₃) 6 1. 46(18H, s), 3. 96(3H, s), 4. 80(2H, s), 6. 23(1H, d, J=9. 2llz), 7. 10(1H, d, J=7. 6llz), 7. 32(1H, dd, J=7. 6, 7. 6Hz), 7. 56(1H, d, J=7. 6Hz), 7. 60(1H, s), 8. 42(1H, d, J=9. 2llz), 10. 63(1H, brs)	'H-NWR (CDC1 ₁) 6 1. 45 (18H, s), 3. 85 (3H, s), 3. 90 (3H, s). 4. 84 (2H, s), 6. 17 (1H, d, J=9. 2Hz), 6. 85 (1H, d, J=8. 6Hz), 7. 34 (1H, d, J=2. 3Hz), 7. 46 (1H, dd, J=8. 6, 2. 3Hz), 8. 39 (1H, d, J=9. 2Hz), 10. 50 (1H, brs)
Reaction condition	base: (1)	base : (I)	base : (1)	base : (1)
Product	Boc ₃ N NO ₃	Borsh H	Boc, N N OMe	MeO O1N ONe
Halogenated derivative	CI N CI	N O D	O,N OME	O,N OMA
Aniline derivative	Boc,1N NII,	Boc ₁ N NH ₂	Boc,N NII,	MeO NH1
Example	o	13	1.7	2.1

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	·		Y	
Spectral data	'H-NMR (CDC1 ₃) 6 1. 24 (3H, 1, 1=7, 3H ₂), 1, 45 (18H, s), 2, 69 (2H, q, J=7, 3H ₂), 3, 94 (3H, s), 4, 85 (2H, s), 6, 19 (1H, d, J=8, 9 H ₂), 7, 18 (1H, d, J=8, 3H ₂), 7, 32 (1H, d, J=2, 0H ₂), 7, 54 (1H, dd, J=8, 3, 2, 0, H ₂), 8, 40 (1H, d, J=8, 9H ₂)	'H-NWR (CDC1,) 6 1. 30 (3H, 1, 1=7. 3Hz), 1. 30 (9H, s), 2. 85 (2H, q, 1=7. 3Hz), 3. 59 (4H, s), 3. 92 (3H, s), 5. 07 (1H, brs), 6. 18 (1H, d, 1=8. 9Hz), 7. 18-7. 29 (5H, m), 7. 43 (1H, s), 7. 73 (1H, dd, 1=8. 6, 2. 0Hz), 8. 40 (1H, d, 1=8. 9Hz), 10. 58 (1H, brs)	'H-NWR (CDC1 ₁) & 1. 47 (1811, s), 4. 81 (2H, s), 6. 80 (111, d, J=8. 6Hz), 7. 13 (1H, d, J=7. 6Hz), 7. 36 (1H, dd, J=7. 6, 7. 6Hz), 7. 49 (1H, s), 7. 65 (1H, d, J=7. 6Hz), 8. 46 (1H, d, J=8. 6Hz), 10. 24 (1H, brs)	'II-NWR (CDC1 ₂) 6 10 33(11, brs), 8. 40(11, d, J=8. 9Hz), 7. 61 (11, d, J=7. 9Hz), 7. 61 (11, d, J=7. 9Hz), 7. 6Hz), 7. 65 (11, d, J=7. 6Hz), 6. 18(111, d, J=8. 9Hz), 4. 85 (211, s), 3. 76 (3H, s), 2. 27 (3H, s), 1. 45 (18H, s) FAB-MS (\(\alpha\c)\) 489 (\(\alpha\c)\) 41)
Reaction condition	base: (1)	base : (I)	base : (1)	base: (1)
Product	Bocs ^M M OMe	Bochin N OMe	Ber, M. M. M.	Boc;N N OMe
alogenated derivative	O,N C	O ₁ N CO Ne	N ₁ O	O,N COMe
Aniline derivative	Boc,N NH,	BocHIN NH,	Bor, N	Boc ₃ N Me
Example	8	2 5	2.7	4 0 6

Spectral data	'H-NMR(CDCl ₃) & 10.54(1H, brs), 8.39(1H, d, J=9.2Hz), 7.45 (1H, dd, J=8.6, 2.3Hz), 7.30-7.24(1H, m), 6.98(1H, d, J=8.6Hz), 6.16(1H, d, J=9.2Hz), 4.85(2H, s), 3.92(3H, s), 3.10(4H, t, J=5.4Hz), 1.94(4H, t, J=5.4Hz), 1.41(18H, s) FAB-MS(m/z) 544(M+1)	'H-NWR(CDC1 ₃) & 10. 62(111, brs), 8. 42(111, d. 1=8. 911z), 7. 60 (2H, d. 1=8. 6Hz), 7. 21(2H, d. 1=8. 6Hz), 6. 22(1H, d. 1=8. 9Hz), 4. 57(1H, brs), 3. 96(3H, s), 3. 39(2H, d1, 1=6. 9, 6. 9Hz), 2. 81(2H, t, 1=6. 9Hz), 1. 44(9H, s) FAB-MS(m/z) 389(M*1)	'H-NWR(CDC1 ₃) & 11. 20(111, brs), 8. 56(111, d. J=2. 0112), 8. 44 (111, d. J=9. 2112), 7. 00(111, dd. J=8. 3, 2. 0112), 6. 90(111, d. J= 8. 3112), 6. 23(111, d. J=9. 2112), 4. 75(111, brs), 4. 29(211, d. J= 5. 6Hz), 4. 06(311, s), 3. 96(311, s), 1. 46(911, s) FAB-MS(\(\omega\zera\zera\zera\zera\zera\zera\zera\zer	'H-NMR (CDC1 ₃) & 10. 68 (114 brs), 8. 41 (114 d. J=8. 9Hz), 7. 65, (114 s), 7. 58 (114 t. J=7. 9Hz), 7. 33 (114 t. J=7. 9Hz), 7. 22 (1 14 d. J=7. 9Hz), 6. 22 (114 d. J=8. 9Hz), 4. 97 (114 s), 3. 98 (3H ₁ s), 1. 65 (9H ₂ s), 1. 38 (6H ₂ brs) FAB-MS (m/z) 403 (M'+1)
Reaction condition	оме base: (I)	base : (1)	base : (1)	base : (1)
Product	Bors N H N OMe	NHBOK N N OMe	Bochin Con Me M N OME	Bettin Or Books
Halogenated derivative	O,N COM.	O,N OM.	O,N OM.	O,N COMe
Aniline derivative	Boc, N NH,	MIB& NH1,	Bociin Nit,	BocHIN NIII,
Ехашр І е	407	4 0 8	4 0 9	4 1 0

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	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
BocsN	Me NH ₁	O,N COMe	Boc,1N H N OMe	оме base: (I)	'H-NMR (CDC1 ₃) & 10, 60(114, br), 8, 40(111, d, 1=8, 9112), 7, 44(114, s), 7, 37(114, s), 6, 92(114, s), 6, 21(111, d, 1=8, 912), 4, 76(214, s), 3, 97(311, s), 2, 35(314, s), 1, 46(1811, s) FAB-MS (m/z) 489 (W*1)
ВосНИ	NH1,	O ₂ N COME	Bocifin N OMe	base: (1)	'H-NWR (CDC1,) Ø 10. 45(1H, brs), 8. 41(1H, d, 1=9. 2Hz), 7. 83 (1H, d, 1=7. 3Hz), 7. 25(2H, m), 7. 21(1H, d, 1=7. 3Hz), 6. 20(1H, d, 1=9. 2Hz), 4. 67(1H, brs), 3. 81(3H, s), 3. 39(2H, d1, 1=6. 9. 6. 9Hz), 2. 89(2H, t, 1=6. 9Hz), 1. 39(9H, s)
Boc ₂ N	NH1, OMe	O ₂ N CI N OMe	Boc, N N OMe	base: (1)	'H-NWR (CDC1,) & 11. 24(1H, brs), 8. 45(1H, d. 1=9. 2Hz), 8. 42 (1H, d. 1=7. 9Hz), 7. 12(1H, dd. 1=7. 9, 7. 6Hz), 6. 95(1H, d. 1=7. 6Hz), 6. 26(1H, d. 1=9. 2Hz), 4. 94(2H, s), 4. 04(3H, s), 3. 87(3H, s), 1. 46(18H, s)
Boczk	in in in in in in in in in in in in in i	O,N COME	Boc, N CI CO, N COME	base: (1)	'H-NMR (CDC1 ₃) & 10, 59 (1H, brs), 8, 41 (1H, d, J=9, 2Nz), 7, 54 ² . (IH, dd, J=8, 6, 2, 3Nz), 7, 39 (1N, d, J=2, 3Nz), 7, 35 (1N, d, J=8, 6Hz), 6, 24 (1H, d, J=9, 2Hz), 4, 93 (2H, s), 3, 94 (3N, s), 1, 45 (18H, s)

			, 	,,,
Spectral data	'H-NMR(CDCI ₃) & 10. 59(1H, brs), 8. 40(1H, d. J=9. 2Hz), 7. 57 (1H, d. J=2. 0Hz), 7. 46(1H, dd. J=7. 9. 2. 0Hz), 7. 11(1H, d. J= 7. 9Hz), 6. 21(1H, d. J=9. 2Hz), 4. 75(1H, brs), 4. 33(2H, d. J= 5. 6Hz), 3. 96(3H, s), 2. 32(3H, s), 1. 47(9H, s)	'II-NUR (CDC1 ₃) & 10. 53 (1H, brs), 8. 41 (1II, d. 1=9. 2Hz), 7. 67 (1H, d. 1=8. 9Hz), 7. 52-7. 43 (1H, m), 7. 05 (1H, dd. 1=9. 2, 8. 9 llz), 6. 23 (1II, d. 1=9. 2Hz), 4. 92 (1H, brs), 4. 38 (2II, d. 1=6. 3 llz), 3. 94 (3H, s), 1. 45 (9II, s)	'II-NIR(CDC1 ₃) 6 11. 24(111, brs), 8. 46(111, d. 1-8. 9112), 8. 43 (111, d. 1-7. 9112), 7. 11(111, dd. 1-8. 3, 7. 9112), 6. 93(111, d. 1-8. 3112), 6. 25(111, d. 1-8. 9112), 4. 93(211, s), 4. 04(311, s), 3. 96(211, q. 1-6. 9112), 1. 52(311, 1, 1-6. 9112), 1. 45(1811, s)	'II-NMR (CDC1,) 6 1. 47 (18H, s). 2. 26 (3H, s), 4. 80 (2H, s), 7. 6. 59 (1H, d, J=8. 6Hz), 6. 97 (1H, s), 7. 14-7. 21 (3H, m), 7. 36 (1H, dd, J=7. 6, 7. 6Hz), 8. 10 (1H, d, J=8. 6Hz)
Reaction condition	base; (I)	base : (1)	base : (1)	base : (1)
Product	Boctin No Na	Boctin Co, N S S S S S S S S S S S S S S S S S S	Boc,14 Come	Bor, N N N
Halogenated derivative	O,N COME	O,N OME	O,N OME	O,N
Aniline derivative	Me N	BocHN NII,	Boc,N NH,	Boc,N
Example	4 1 5	4 1 6	417	4 1 8

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Table 43

Spectral data	'H-NMR(CDCI,) 6 1. 46(18H, s), 3. 74(3H, s), 4. 79(2H, s), 6. 34(1H, dd, J=9, 6, 2. 6Hz), 6. 57(1H, dd, J=2. 6Hz), 7. 14-7. 20(2H, m), 7. 24(1H, s), 7. 37(1H, dd, J=7. 6, 7. 6Hz), 8. 18(1H, d, J=9. 6Hz), 9. 77(1H, brs)	'H-NWR (CDC1 ₃) 6 1. 44 (18H, s), 3. 70 (3H, s), 3. 86 (3H, s). 4. 81 (2H, s), 6. 27 (1H, dd, J=9. 6, 2. 6Hz), 6. 33 (1H, d, J=2. 6 Hz), 6. 89 (1H, d, J=8. 3Hz), 7. 03 (1H, d, J=2. 0Hz), 7. 11 (1H dd, J=8. 3, 2. 0Hz), 8. 16 (1H, d, J=9. 6Hz), 9. 66 (1H, s)
Reaction condition	base: (1)	base : (2)
Product	Bocs ^N OMe	Bocy ^N H OMe
Halogenated derivative	d O'IN	O,N
Aniline	Boc ₁ N NII ₁	Mro Mri
Example	4 1 9	4 2 0

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Example 2

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Synthesis of 2-(3-aminomethylphenylamino)-3-nitropyridine hydrochloride

[0057] A mixture of the compound (95.2 mg) obtained in Example 1 and trifluoroacetic acid (2 ml) was stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 ml) and a 1.4-dioxane solution (4 N, 0.5 ml) of hydrogen chloride was added at room temperature and the mixture was concentrated under reduced pressure. In addition, the resulting residue was recrystallized from ethanol-ethyl acetate to give 56.7 mg of the titled compound (yield, 94%)

1H-NMR(DMSO-d₆) δ:4.03(2H, q, J=5.6Hz), 7.03(1H dd, J=8.2, 4.3Hz), 7.28(1H, d, J=7.6Hz), 7.42(1H, dd, J=7.6, 7.6Hz), 7.74(1H, s), 7.75(1H, d, J=7.6Hz), 8.46(3H, brs), 8.50-8.60(2H, m), 10.00(1H, s)

15 [0058] The procedure of Example 2 was repeated using corresponding reagents to give the compounds shown in Tables 44 - 62.

Table 44

Spectral data	'H-NAR (DMSO-d ₆) & 3. 52 (3H, brs), 4. 03 (2H, q. J=5. 6Hz), 6. 95 (1H, dd, J=7. 0, 7. 0Hz), 7. 28 (1H, d, J=7. 9Hz), 7. 33-7. 40 (3H, m), 7. 48 (1H, d, J=7. 9Hz), 7. 58 (1H, s), 8. 52 (3H, brs), 10. 22 (1H, brs)	'H-NWR (DMSO-d ₄) & 1. 30 (3H, 1, 1=6. 9Hz), 3. 21 (2H, q, 1=6. 9Hz), 4. 04 (2H, q, 1=6. 9Hz), 7. 01 (1H, dd, 1=7. 9, 5. 9Hz), 7. 10 (1H, d, 1=7. 3Hz), 7. 35 (1H, d, 1=5. 9Hz), 7. 39 (1H, dd, 1=7. 3, 7. 3Hz), 7. 41 (1H, d, 1=7. 3Hz), 7. 50 (1H, d, 1=7. 9Hz), 7. 59 (1H, s), 8. 57 (3H, brs), 10. 55 (1H, brs)	'H-NMR (DMSO-d ₄) & 4. 01 (2H, q, J=5, 6Hz), 7. 08 (1H, d, J=9, 6Hz), 7. 23 (1H, d, J=7, 6Hz), 7. 41 (1H, dd, J=7, 6, 7, 6Hz), 7. 74 (1H, d, J=7, 6Hz), 7. 85 (1H, s), 8. 31 (1H, dd, J=9, 6, 2, 6Hz), 8. 47 (3H, brs), 9. 04 (1H, d, J= 2. 6Hz), 10. 52 (1H, s)	'H-NMR (DMSO-d ₆) & 3. 99 (2H, q, J=5. 3Hz), 7. 14 (1H, d, J=7. 6Hz), 7. 14 (IH, d, J=8. 9Hz), 7. 36 (1H, dd, J=7. 6, 7. 6Hz), 7. 53 (1H, d, J=7. 6Hz), 7. 67 (1H, d, J=8. 9Hz), 7. 73 (1H, s), 8. 10 (1H, s), 8. 49 (3H, brs), 9. 87 (IH, brs)
Product	2HG H3N N	HO N HE	HCI H3N NO1	2HCI NH3
Reagent	Bossin Han N	Boc, N N HEA	Boc3N NO. H. NO.	Bocs ^M H
Example	4	8	10	1 2

Example	Reagent	Product	Spectral data
4	Boc ₂ N N N	HCI OO'N HE HIN H	'H-NWR(DWSO-d ₆) & 2. 36(3H, s), 3. 97(2H, q, 1=5. 6Hz), 6. 91(1H, d, 1=5. 0Hz), 7. 19(1H, d, 1=7. 6Hz), 7. 34(1H, dd, 1=7. 6, 7. 6Hz), 7. 55(1H, d, 1=7. 6Hz), 7. 63(1H, s), 8. 20(1H, d, 1=5. 0Hz), 8. 48(3H, brs), 9. 08(1H, s)
16	BocsN H H	2HCI H3N H3N H3N H3N H3N H3N H3N H3N H3N H3N	¹ H-NWR (DMSO-d ₄) & 2. 26 (3H, s), 3. 56 (3H, brs), 4. 03 (2H, q. J=5. 6Hz). 6. 96 (1H, d, J=5. 9Hz), 7. 30-7. 38 (3H, m), 7. 48 (1H, dd, J=7. 9. 7. 9Hz), 7. 53 (1H, s), 8. 58 (3H, brs), 10. 23 (1H, brs)
1 8	Boc;N H N OMe	HO N H N N'H	'H-NWR(DMSO-d ₁) & 3. 92(3H, s), 4. 03(2H, s), 6. 41(1H, d, J=9. 2Hz), 7. 31(1H, d, J=7. 9Hz), 7. 45(1H, dd, J=7. 9, 7. 9Hz), 7. 77-7. 87(2H, m), 8. 46(1H, d. J=9. 2Hz), 8. 48(3H, brs), 10. 49(1H, brs)
2 0	Borin Hill N OME	2HC H,N H,N OM.	'H-NMR (DMSO-d ₁) & 3. 83 (3H, s), 3. 98 (2H, s), 6. 33 (1H, d, I=8. 6Hz), 7. 09 (1H, d, I=7. 3Hz), 7. 36 (1H, dd, I=7. 3, 7. 3Hz), 7. 61 (1H, d, I=7. 3Hz), 7. 63 (1H, d, I=8. 6Hz), 7. 76 (1H, s)

Table 46

Example	Reagent	Product	Spectral data
2 2	Bos, N H N OMe	MeO OrN N OMe	'H-NWR (DMSO-d ₆ ,) 6 3. 86 (3H, s), 3. 89 (3H, s), 3. 98 (2H, s), 6. 36 (1H, d, J=8. 9Hz), 7. 12 (1H, d, J=8. 9Hz), 7. 71 (1H, s), 7. 77 (1H, d, J=8. 9Hz), 8. 31 (3H, brs), 8. 43 (1H, d, J=8. 9Hz), 10. 42 (1H, s)
2.4	Boc ₁ N Boc ₁ N Boc ₁ N Boc ₂ N	H ₃ N N N OME	¹ H-NMR (DMS0-d ₄) & 1. 19 (3H, 1, J=7, 6Hz), 2. 70 (2H, q, J=7, 6Hz), 3. 94 (3H, s), 4. 04 (2H, s), 6. 40 (1H, d, J=9. 2Hz), 7. 31 (1H, d, J=8. 6Hz), 7. 71 (1H, d, J=1, 3Hz), 7. 84 (1H, dd, J=8. 6, 1, 3Hz), 8. 40 (3H, brs), 8. 46 (1H, dd, J=9. 2Hz), 10. 50 (1H, s)
2 6	BochN N OMe	H ₂ N HC HC HC	'H-NMR (DMSO-d ₁) & 1. 22 (3H, 1, J=7. 3Hz), 2. 59 (2H, q. J=7. 3Hz), 3. 63 (4H, s), 3. 94 (3H, s), 6. 42 (1H, d, J=9. 2Hz), 7. 29-7. 44 (5H, m), 7. 52 (1H, s), 8. 05 (1H, d, J=8. 6Hz), 8. 47 (1H, d, J=9. 2Hz), 8. 68 (3H, brs), 10. 55 (1H, s)
2 8	Boc, N Co	HG GoN No.	'H-NMR (DMSO-d ₆) & 4. 03 (2H, s), 7. 05 (1H, d, J=8. 6Hz), 7. 35 (1H, d, J=7. 6Hz), 7. 47 (1H, dd, J=7. 6, 7. 6Hz), 7. 62 (1H, s), 7. 73 (1H, d, J=7. 6Hz), 8. 48 (3H, bfs), 8. 57 (1H, d, J=8. 6Hz), 10. 15 (1H, s)

Spectral data	¹ H-NMR (DMS0-d ₆) 6 2. 93 (3H, s), 4. 04 (2H, s), 6. 19 (1H, d, J=9. 2Hz), 7. 24 (1H, d, J=7. 6Hz), 7. 44 (1H, dd, J=7. 6, 7. 6Hz), 7. 80 (1H, s), 7. 98 (1H, d, J=7. 6Hz), 8. 10 (1H, d, J=9. 2Hz)	14-NWR (DMS0-d ₁) 6 1. 17 (3H, 1, 1=7. 3Hz), 3. 40 (2H, q, 1=7. 3Hz), 4. 01 (2H, q, 1=5. 3Hz), 6. 06 (1H, brs), 6. 19 (1H, d, 1=9. 2Hz), 7. 26 (1H, d, 1= 7. 3Hz), 7. 42 (1H, dd, 1=7. 3, 7. 3Hz), 7. 77 (1H, s), 7. 93 (1H, d, 1=7. 3Hz) N NHES 9, 8. 09 (1H, d, 1=9. 2Hz), 8. 52 (3H, brs), 10. 98 (1H, s)	'H-NMR (DMSO-d ₁) 6 0. 92 (3H, 1, 1=7, 3Hz), 1. 55-1. 63 (2H, m), 3. 29-3. 40 (2H, m), 4. 01 (2H, q, 1=5, 3Hz), 6. 10 (1H, brs), 6. 21 (1H, d, 1=9, 2Hz), 7. 27 (1H, d, 1=7, 6Hz), 7. 41 (1H, dd, 1=7, 6Hz), 7. 73 (1H, s), 7. 97 (1H, d, 1=7, 6Hz), 8. 09 (1H, d, 1=9, 2Hz), 8. 53 (3H, brs), 10. 98 (1H, s)	'H-NMR (DMSO-d _e) & 3. 19 (6H, s), 4. 01 (2H, s), 6. 40 (1H, d, J=9. 6Hz), 7. 26 (1H, d, J=7. 6Hz), 7. 42 (1H, dd, J=7. 6, 7. 6Hz), 7. 75 (1H, s), 7. 88 (1H, d, J=7. 6Hz), 8. 21 (1H, d, J=9. 6Hz), 8. 46 (3H, brs), 10. 78 (1H, s)
Product	H, N H, N H, N H, N H, N H, N H, N H, N	HO ON HEN HED	HJW NHPP	HG O'N H
Reagent	Becyn Charles H N NHMe	Box 5.N A HELL	Bocs,N H NIHPr	Bors ^{IM} N NIMes
Example	3 0	80 80	& 4	3 6

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Spectral data	¹ H-NMR (DMSO-d ₄) & 4. 01 (2H, s), 6. 93 (1H, d, J=8. 1Hz), 7. 21 (1H, d, J=7. 6Hz), 7. 6Hz), 7. 42 (1H, dd, J=7. 6, 7. 6Hz), 7. 55 (1H, s), 7. 93 (1H, d, J=7. 6Hz), 8. 25 (1H, d, J=8. 1Hz), 8. 46 (3H, brs), 10. 66 (1H, s)	'H-NMR (DMSO-d ₄) & 3. 88 (3H, s), 3. 94 (2H, q, J=5. 6Hz), 6. 16 (1H, d, J=7. 9Hz), 6. 49 (1H, d, J=7. 9Hz), 6. 62 (2H, brs), 7. 05 (1H, d, J=7. 6Hz), 7. 30 (1H, dd, J=7. 6, 7. 6Hz), 7. 49 (1H, dd, J=7. 9, 7. 9Hz), 7. 63 (1H, d, J=7. 6Hz), 7. 80 (1H, s), 8. 50 (3H, brs)	'H-NMR (DMSO-d _b) & 3. 41 (2H, s), 6. 39 (1H, dd, 1=7. 3, 5. 9Hz), 6. 68-6. 89 (4H, m), 7. 35 (1H, d, 1=5. 9Hz), 7. 67 (1H, d, 1=7. 3Hz)	'H-NMR (DMSO-d ₆) 6 3. 87 (3H, s), 3. 95 (3H, s), 4. 01 (2H, brs), 6. 29 (1H, d, J=8. 6Hz), 7. 15 (1H, d, J=7. 6Hz), 7. 40 (1H, dd, J=7. 9, 7. 6Hz), 7. 74 (1H, s), 7. 88 (1H, d, J=7. 9Hz), 8. 16 (1H, d, J=8. 6Hz), 8. 30 (3H, brs), 10. 47 (1H, s)
Product	HC N N ₄ H	2HG OME	2HC H,N H	HCI N N H CO ₂ Me
Reagent	Bociny N	Boc ₂ N N	Boc ₃ N H H	Boc ₃ N OMe CO ₃ Me
Example	8 8	4 0	4 2	4. 4.

Example	Reagent	Product	Spectral data
57	Boc, N C H N OEr	H2 O3N H3N H3N H3N H3N H3N H3N H3N H3N H3N H	'H-NMR (DMS0-d ₆) & 1. 32 (3H, t, J=7. 3Hz), 4. 03 (2H, s), 4. 36 (2H, q, J=7. 3Hz), 6. 39 (1H, d, J=8. 9Hz), 7. 31 (1H, d, J=7. 6Hz), 7. 45 (1H, dd, J=7. 6, 7. 6Hz), 7. 75 (1H, s), 7. 79 (1H, d, J=7. 6Hz), 8. 45 (1H, d, J=8. 9Hz), 8. 45 (3H, brs), 10. 49 (1H, s)
6 1	BocHIN H N SIMe	HG ON N	'H-NWR(DWSO-d ₆) 6 3. 33(3H, s), 4. 03(2H, s), 6. 91(1H, d, J=8. 9Hz), 7. 31(1H, d, J=7. 6Hz), 7. 45(1H, dd, J=7. 6, 7. 6Hz), 7. 72-7. 79(2H, m), 8. 34(1H, d, J=8. 9Hz), 8. 44(3H, brs), 10. 33(1H, s)
7.7	BocHN H N OMe	H ₃ N N OMe	¹ H-NMR (DMSO-d ₆)
108	BocHN H N OM:	HC OHC HIN OME	'H-NNR (DMSO-d ₆) & 3. 99 (3H, s), 4. 04 (2H, q, J=5, 6H ₂), 6. 40 (1H, d, J=8. 6H ₂), 7. 19 (1H, d, J=7. 9H ₂), 7. 43 (1H, dd, J=7. 9, 7. 9H ₂), 7. 74 (1H, s), 7. 97 (1H, d, J=7. 9H ₂), 8. 09 (1H, d, J=8. 6H ₂), 8. 27 (3H, brs), 9. 78 (1H, s), 10. 96 (1H, s)

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Spectral data	'H-NWR(DMSO-d ₆) & 2. 28(3H, s), 4. 03(2H, s), 6. 75(1H, d, J=8. 9Hz), 7. 08(1H, s), 7. 27-7. 36(2H, m), 7. 42-7. 49(2H, m), 8. 04(1H, d, J=8. 9 Hz), 8. 30(3H, brs), 9. 40(1H, s)	¹ H-NMR (DMSO-d ₆) δ 3. 77 (3H, s), 4. 05 (2H, q, J=4. 6Hz), 6. 53 (1H, dd, J= 9. 2, 2. 3Hz), 6. 60 (1H, d, J=2. 3Hz), 7. 34 (1H, d, J=7. 6Hz), 7. 39 (1H, d, J=7. 6Hz), 7. 48 (1H, dd, J=7. 6, 7. 6Hz), 7. 54 (1H, s), 8. 15 (1H, d, J=9. 2 OM• Hz), 8. 46 (3H, brs), 9. 65 (1H, s)	H2), 7. 87 (1H, s), 7. 62-7. 54 (1H, m), 7. 41 (1H, dd, J=7. 9, 7. 6H2), 7. 22 (1H, d, J=7. 6H2), 6. 61 (1H, d, J=8. 9H2), 4. 06 (3H, s), 4. 01 (2H, brs) FAB-MS (m/z) 275 (W+1)	'H-NMR (DMSO-d ₆) & 10. 34 (1H, brs), 8. 43 (1H, d, J=8. 9Hz), 8. 42-8. 20 (4H, m), 7. 77 (1H, dd, J=5. 0, 4. 6Hz), 7. 32 (1H, d, J=4. 6Hz), 6. 33 (1H, d, J=8. 9Hz), 4. 11 (2H, s), 3. 72 (3H, s), 2. 29 (3H, s) FAB-MS (m/z) 289 (M*1)
Product	HG O ₃ N H	HG GNN H	HG H H OME	HC O'N H
Reagent	Bor, N N H	Boc;N H OMe	Boc, N N OMe	Bocs IN COAN NO OME
Example	151	153	457	4 5 8

Spectral data	'H-NuR (Duso-d _b) 6 10. 52 (1 H, brs), 8. 45 (1 H, d, J=9. 2Hz), 8. 45-8. 28 (4 H, m), 8. 02-7. 73 (2 H, m), 7. 40 (1 H, brs), 6. 40 (1 H, d, J=9. 2Hz), 4. 23 (2 H, s), 3. 94 (3 H, s), 3. 50-3. 20 (4 H, m), 2. 21-1. 95 (4 H, m) FAB-MS (m/z) 344 (M*1)	'H-NMR (DMSO-d ₄) 6 10. 50 (1H, s), 8. 44 (1H, d, J=8. 9Hz), 7. 98 (3H, brs). 7. 69 (2H, d, J=7. 9Hz), 7. 28 (2H, d, J=7. 9Hz), 6. 36 (1H, d, J=8. 9Hz), 3. 92 (3H, s), 3. 15-2. 97 (2H, m), 2. 93 (2H, t, J=7. 6Hz) OMe FAB-MS (m/z) 289 (M'+1)	'H-NWR (DMSO-d ₆) & 11. 06 (1H, s), 8. 63 (1H, s), 8. 46 (1H, d, J=8. 9Hz), 8. 33 (3H, brs), 7. 57 (1H, d, J=7. 3Hz), 7. 15-7. 10 (1H, m), 6. 38 (1H, d, J=8. 9Hz), 4. 08 (2H, s), 3. 98 (6H, s) FAB-MS (m/z) 305 (M*+1)	'H-NMR (DMSO-d ₆) & 10. 52(1H, s). 8. 57(3H, brs), 8. 46(1H, d, J=9. 2H2). 7. 84(1H, d, J=7. 9Hz), 7. 75(1H, s), 7. 47(1H, dd, J=8. 2, 7. 9Hz), 7. 42- 7. 35(1H, m), 6. 41-6. 37(1H, m), 3. 91(3H, s), 1. 67(6H, s) FAB-MS(m/z) 303(M*+1)
Product	H,N M OME	NH, N, OMe	HCI O'N OME H OME	HG ON H
Reagent	Bec; N N OM.	NHBo O,N N	BocHN One H OMe	Bechin Con H
Example	4 5 9	4 6 0	461	4 6 2

Table 52

Spectral data	'H-NMR (DMSO-d _b) 6 10. 49 (1H, s), 8. 45 (1H, d, J=8. 9Hz), 8. 35 (3H, brs), 7. 68 (1H, s), 7. 61 (1H, s), 7. 12 (1H, s), 6. 40 (1H, d, J=8. 9Hz), 3. 99 (2H, s), 3. 95 (3H, s), 2. 36 (3H, s) FAB-MS (m/z) 289 (M*1)	'H-NMR(DMSO-d ₆) & 10.20(IH, brs), 8.43(IH, d, J=9.2Hz), 7.95(3H, brs), 7.50(IH, dd, J=7.9, 1.7Hz), 7.40-7.25(3H, m), 6.30(IH, d, J=9.2 Hz), 3.58(3H, s), 3.03-2.88(4H, m) FAB-MS(m/z) 289(M*1)	'H-NMR(DMSO-d ₆) & 11.09(1H, s), 8.58-8.53(1H, m), 8.51(1H, d, J=9.2 Hz), 8.40(3H, brs), 7.32-7.28(2H, m), 6.46(1H, d, J=9.2Hz), 4.11(2H, s), 4.01(3H, s), 3.84(3H, s) FAB-MS(m/z) 305(M*1)	'H-NWR(DMSO-d ₆) 5 10. 51 (1H brs), 8. 50 (3H brs), 8. 47 (1H d, J=9. 2Hz), 7. 93-7. 89 (2H m), 7. 55 (1H d, J=9. 2Hz), 6. 43 (1H d, J=9. 2Hz), 4. 14 (2H, s), 3. 93 (3H, s) FAB-MS(m/z) 309 (M*+1)
Product	HCI CON NO CONCE	HCI HCI HCI HCI HCI HCI HCI HCI HCI HCI	HCI O'N HIN OME HIN OME	H ₃ N N N OME
Reagent	Bor 3.N N OMe	BocHN H N OMe	Bess N N OMe	Bec;N N N ONe
Ехапріе	4 6 3	464	465	466

Reagent Product Spectral data	H-NMR (DMSO-d _a) & 10. 45 (1H brs), 8. 58-8. 37 (4H, m), 7. 87-7. 79 (2H, m) and the set of the se	(H-NWR (DMSO-d ₄) 5 11. 10 (1H, s), 8. 57-8. 53 (1H, m), 8. 50 (1H, d, J=9. 2 Hz), 8. 37 (3H, brs), 7. 35-7. 24 (2H, m), 6. 46 (1H, d, J=9. 2Hz), 4. 10 (2H, m), 0. 4. 01 (3H, s), 3. 96 (2H, q, J=6. 9Hz), 1. 45 (3H, t, J=6. 9Hz)	HC	CO, Me HG HG HG HG HG HG HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HG HgN HGN HgN HGN HgN HGN HgN HGN HgN HGN HgN HgN HGN HgN HgN HGN HgN HgN HgN HgN HgN HgN HgN HgN HgN Hg
Reagent	Bochin K H	Bocs N OER H N OI	Boc ₂ N O ₂ N O ₃	Bechin Co.Me
Example	467	4 6 8	4 6 9	470

Table 54

Spectral data	'H-NMR (DMSO-d _e) & 13. 28 (1H, brs), 9. 47 (1H, s), 8. 34 (3H, brs), 7. 79 (1H, s), 7. 65 (1H, d, J=8. 6Hz), 7. 33 (1H, dd, J=8. 6, 7. 3Hz), 7. 06 (1H, d, J=7. 3Hz), 6. 96 (1H, s), 6. 53 (1H, s), 3. 97 (2H, d, J=5. 3Hz), 3. 92 (3H, s)	¹ H-NMR (D ₄ 0) & 7. 63-7. 52 (1H, m), 7. 45-7. 37 (3H, m), 6. 54 (1H, s), 6. 41 (1H, s), 4. 22 (2H, s), 4. 02 (3H, s), 2. 37 (3H, s)	'H-NMR (DMSO-d ₆) & 9. 89 (1H, brs), 8. 43 (3H, brs), 8. 38 (1H, d, J=5. 3Hz), 7. 83 (1H, s), 7. 73 (1H, d, J=7. 9Hz), 7. 34 (1H, dd, J=7. 9, 7. 6Hz), 7. 13 (1H, d, J=7. 6Hz), 6. 82 (1H, d, J=5. 3Hz), 3. 97 (2H, q, J=5. 6Hz), 2. 41 (3H, s)
Product	HCO N H N OWE	2HG Me H ₂ N N OMe	2HCl
Reagent	Bottin H N OMe	Beethin H N OMe	Bochin H H
Example	471	473	474

Table 55

Example	Reagent	Product	Spectral data
475	Boc, N N ONAe	2HC H ₃ N N OMe	'H-NMR (DMSO-d ₆) 6 3. 78 (3H, s), 3. 98 (2H, s), 6. 33 (1H, d, J=8. 2Hz), 7. 18 (1H, d, J=7. 6Hz), 7. 35 (1H, dd, J=7. 6, 7. 6Hz), 7. 57 (1H, d, J=7. 6Hz), 7. 69 (1H, s), 7. 84 (1H, d, J=8. 2Hz), 8. 16 (1H, s), 8. 37 (3H, brs)
476	BocHIN O H	HG O'N OMe	¹ H-NMR (DMSO-d ₆) 6 3. 81 (3H, s), 3. 98 (2H, s), 7. 17 (1H, d, J=7. 6Hz), 7. 21 (1H, d, J=7. 6Hz), 7. 25 (1H, dd, J=9. 2, 3. 0Hz), 7. 32 (1H, s), 7. 38 (1H, dd, J=7. 6, 7. 6Hz), 7. 39 (1H, d, J=9. 2Hz), 7. 57 (1H, d, J=3. 0Hz), 8. 36 (3H, brs), 9. 02 (1H, s)
477	Bociin H H Me	HG O,N H,N Me	¹ H-NMR (DMSO-d _b) & 2. 18 (3H, s), 3. 87 (2H, s), 6. 58 (1H, d, J=7. 9Hz), 6. 63 (1H, s), 6. 87 (1H, d, J=7. 6Hz), 7. 18 (1H, dd, J=7. 6, 7. 6Hz), 7. 32 (1H, dd, J=7. 9, 7. 9Hz), 7. 62 (1H, d, J=7. 6Hz), 7. 80 (1H, d, J=7. 9Hz). 8. 12 (1H, s), 8. 28 (3H, brs)
478	BocHN	2HG Me	'H-NMR(DMSO-d ₆) & 2. 40 (3H, s), 4. 05 (2H, q, J=5. 3Hz), 6. 93 (1H, d, J=6. 3Hz), 7. 14 (1H, s), 7. 34-7. 39 (2H, m), 7. 49 (1H, dd, J=7. 6, 7. 6Hz), 7. 62 (1H, s), 8. 02 (1H, d, J=6. 3Hz), 8. 59 (3H, brs), 10. 83 (1H, brs)

Table 56

Example	Reagent	Product	Spectral data
479	Boehn Me H N	2HC H,N Mc Me H	'H-NMR (DMSO-d ₆) & 1. 66 (6H, s), 2. 38 (3H, s), 6. 90 (1H, d, J=6. 3Hz), 7. 04 (1H, s), 7. 40-7. 53 (3H, m), 7. 62 (1H, s), 8. 00 (1H, d, J=6. 3Hz), 8. 76 (3H, brs), 10. 52 (1H, brs)
480	Bocfin H Me	ZHCI H ₂ N H N	'H-NMR (DMSO-d ₂) 5 0. 81 (3H, 1, J=7, 3Hz), 1. 83-2. 06 (2H, m), 2. 39 (3H, s), 4. 10-4. 25 (1H, m), 6. 92 (1H, d, J=6. 3Hz), 7. 11 (1H, s), 7. 37 (1H, d, J=7, 6Hz), 7. 50 (1H, dd, J=7, 6Hz), 7. 60 (1H, s), 8. 02 (1H, d, J=6. 3Hz), 8. 69 (3H, brs), 10. 76 (1H, brs)
481	Boc ₂ N Me H N	2HG H ₃ N Me H	'H-NMR (DMSO-d ₆)
4 8 2	BocHN H	EI N N N N N N N N N N N N N N N N N N N	'H-NMR (DMSO-d ₁) 6 1. 20(3H, 1, 1=7. 6Hz), 2. 41(3H, s), 2. 72(2H, q, J=7. 6Hz), 4. 07(2H, q, J=5. 6Hz), 6. 92(1H, d, J=6. 3Hz), 7. 12(1H, s), 7. 30(1H, d, J=8. 3Hz), 7. 35(1H, d, J=8. 3Hz), 7. 57(1H, s), 8. 00(1H, d, J=6. 3Hz), 8. 61(3H, brs), 10. 79(1H, brs)

Example	Reagent	Product	Spectral data
4 8 3	Eto Me Boctin H	EtO Hz	'H-NMR (DMSO-d ₆) & 1. 40 (3H, t, J=6. 9Hz), 2. 38 (3H, s), 3. 99 (2H, q. J=5. 3Hz), 4. 13 (2H, q. J=6. 9Hz), 6. 87 (1H, d. J=6. 3Hz), 7. 03 (1H, s), 7. 15 (1H, d. J=8. 9Hz), 7. 33 (1H, dd. J=8. 9, 1. 7Hz), 7. 51 (1H, d. J=1. 7Hz), 7. 94 (1H, d. J=6. 3Hz), 8. 48 (3H, brs), 10. 72 (1H, brs)
484	BocHN H	2HC H N N	'H-NWR (DMSO-d ₆) 6 2.37 (3H, s), 2.88-3.10 (4H, m), 6.88 (1H, d, J=6.6 Hz), 6.95 (1H, s), 7.39-7.50 (4H, m), 7.89 (1H, d, J=6.6Hz), 8.12 (3H, brs), 10.69 (1H, brs)
4 8 5	Boctin C H N	H,N C H	'H-NWR (DMSO-d _s) & 2.39(3H, s), 4.19(2H, q, J=5.0Hz), 6.93(1H, d, J=6.3Hz), 6.98(1H, s), 7.48-7.68(3H, m), 7.97(1H, d, J=6.3Hz), 8.71(3H, brs), 10.56(1H, brs)
4 8 6	BocHN N N Me	2HCI Me H ₃ N N N Me	'H-NMR (DMSO-d ₆) & 2. 35 (3H, s), 2. 49 (3H, s), 4. 05 (2H, q, J=5. 3Hz), 6. 82 (1H, s), 7. 00 (1H, s), 7. 33-7. 38 (2H, m), 7. 48 (1H, dd, J=7. 6, 7. 6Hz), 7. 56 (1H, s), 8. 58 (3H, brs), 10. 30 (1H, brs)

Table 58

Example	Reagent	Product	Spectral data
487	BocHN	2HC H ₂ N H	'H-NMR (DMSO-d _b) & 1. 20(3H, 1, 1=7. 3Hz), 2. 71(2H, q, 1=7. 3Hz), 4. 05 (2H, q, 1=5. 3Hz), 6. 98(1H, d, 1=6. 3Hz), 7. 18(1H, s), 7. 34-7. 42(2H, m), 7. 49(1H, dd, 1=7. 6, 7. 6Hz), 7. 64(1H, s), 8. 03(1H, d, 1=6. 3Hz), 8. 66 (3H, brs), 11. 00(1H, brs)
4 8 8	BocHN	2HC Me	'H-NMR (DMSO-d ₆) & 1. 73-1. 85(1H, m), 2. 15-2. 27(1H, m), 2. 40(3H, s), 2. 56-2. 66(4H, m), 6. 92(1H, d, J=6. 3Hz), 7. 13(1H, s), 7. 35-7. 42(2H, m), 7. 53(1H, dd, J=7. 6, 7. 6Hz), 7. 63(1H, s), 8. 00(1H, d, J=6. 3Hz), 8. 94 (3H, brs), 10. 84(1H, brs)
4 8 9	BocHN H	Me Me Me Me Me Me Me Me Me Me Me Me Me M	'H-NWR (DMSO-d ₄) & 2. 37 (3H, s), 2. 87-3. 15 (4H, m), 6. 87 (1H, d, 1=6. 3 Hz), 7. 01 (1H, s), 7. 37 (4H, s), 7. 92 (1H, d, 1=6. 3Hz), 8. 16 (3H, brs), 10. 65 (1H, brs)
4 9 0	Boc ₂ N N N N	2HG Me	'H-NWR (DMSO-d ₁) & 1. 13 (3H, 1, J=6. 9Hz), 2. 40 (3H, s), 3. 86 (2H, q, J=6. 9Hz), 4. 06 (2H, q, J=5. 3Hz), 6. 93 (1H, d, J=5. 9Hz), 7. 07 (1H, s), 7. 28 (1H, dd, J=7. 6, 7. 6Hz), 7. 45 (1H, d, J=7. 6Hz), 7. 51 (1H, d, J=7. 6Hz), 7. 96 (1H, d, J=5. 9Hz), 8. 54 (3H, brs), 10. 71 (1H, brs)

Example	Reagent	Product	Spectral data
491	Boc, N H N	H,N H N SHCI	'H-NUR (DMSO-d ₁) & 2. 41 (3H, s), 4. 14 (2H, q, J=5. 3Hz), 6. 95 (1H, d, J=6. 3Hz), 7. 18 (1H, s), 7. 44 (1H, dd, J=8. 6, 2. 0Hz), 7. 58 (1H, d, J=8. 6Hz), 7. 79 (1H, d, J=2. 0Hz), 8. 04 (1H, d, J=6. 3Hz), 8. 76 (3H, brs), 10. 89 (1H, brs)
492	Bec,14 H N OMe	H.C. N. N. OM.	¹ H-NWR (DMSO-d ₁) & 3. 86 (3H, s), 4. 01 (2H, q, J=5. 9Hz), 6. 36 (1H, d, J=8. 5Hz), 7. 19 (1H, d, J=7. 8Hz), 7. 38 (1H, dd, J=7. 8, 7. 8Hz), 7. 63 (1H, d. J=7. 8Hz), 7. 77 (1H, s), 7. 95 (1H, d, J=8. 5Hz), 8. 41 (3H, brs), 9. 28 (1H, s)
493	BocHN G H	HO Hy N	'H-NMR (DMSO-d ₁) & 3. 98 (2H, q, J=5. 3H ₂), 6. 86 (1H, dd, J=7. 9, 5. 0H ₂), 7. 14 (1H, d, J=7. 6H ₂), 7. 34 (1H, dd, J=7. 6, 7. 6H ₂), 7. 66 (1H, d, J=7. 6H ₂), 7. 76-7. 86 (2H, m), 8. 10 (1H, dd, J=5. 0, I. 3H ₂), 8. 38 (3H, br ₃), 8. 47 (1H, s)
4 9 4	Boc ₂ N OMe CONH ₂	HCI NOWIE	'H-NWR (DMSO-d ₆) & 3. 93 (3H, s), 4. 01 (2H, q, 1=5. 9H ₂), 6. 24 (1H, d, 1=8. 6H ₂), 7. 08 (1H, d, 1=7. 9H ₂), 7. 37 (1H, dd, 1=7. 9, 7. 9H ₂), 7. 42 (1H, brs), 7. 65 (1H, s), 7. 88 (1H, d, 1=7. 9H ₂), 8. 04 (1H, brs), 8. 14 (1H, d, 1=8. 6H ₂), 8. 22 (3H, brs), 11. 76 (1H, s)

Table 60

Spectral data	'H-NWR (DMSO-d ₆) 6 2. 19 (3H, s), 3. 79 (3H, s), 3. 94 (2H, q, J=5. 6Hz). 6. 16 (1H, d, J=7. 6Hz), 7. 03 (1H, d, J=7. 9Hz), 7. 29 (1H, dd, J=7. 9, 7. 9Hz), 7. 36 (1H, d, J=7. 6Hz), 7. 64 (1H, d, J=7. 9Hz), 7. 82 (1H, s), 7. 95 (1H, brs), 8. 35 (3H, brs)	¹ H-NMR (DMSO-d _a) 6 3. 74 (3H, s), 3. 88 (3H, s), 4. 00 (2H, q, J=5. 3Hz), 6. 35 (1H, d, J=2. 3Hz), 6. 46 (1H, dd, J=9. 6. 2. 3Hz), 7. 15 (1H, d, J=8. 6Hz), 7. 43 (1H, s), 8. 13 (1H, d, J=9. 6Hz), 8. 18 (3H, brs), 9. 60 (1H, s)	'H-NMR (DMSO-d _b) & 2. 25 (3H, s), 4. 21 (2H, q, 1=5, 6Hz), 7. 26-7. 50 (4H, m), 7. 62 (1H, s), 7. 88 (1H, d, 1=10, 2Hz), 7. 95 (1H, s), 8. 57 (3H, brs), 10. 77 (1H, brs)	'H-NMR (DMSO-d _b) & 2. 40 (3H, s), 4. 04 (2H, q, J=5. 6Hz), 7. 42 (1H, dd, J=6. 6. 6. 6Hz), 7. 40-7. 57 (3H, m), 7. 66 (1H, s), 7. 90-7. 99 (2H, m), 8. 65 (3H, brs), 9. 77 (1H, brs)
Product	2HC H, N N OM.	MeO Q PIN HJN HG HG	B ₁ N H	ZHC Me H
Reagent	BecHN H N OMe	MeO O3M Dose	Boc, N H H N	BocHV M. H
Example	495	496	501	5 0 2

Table 61

Spectral data	'H-NMR (CDC1 ₃) & 2. 38 (3H, s), 3. 88 (3H, s), 3. 99 (2H, q. 1=5. 6Hz), 6. 87 (1H, d, 1=6. 3Hz), 7. 02 (1H, s), 7. 17 (1H, d, 1=8. 6Hz), 7. 36 (1H, dd, 1=8. 6. 2. 0Hz), 7. 51 (1H, d, 1=2. 0Hz), 7. 94 (1H, d, 1=6. 3Hz), 8. 46 (3H, brs), 10. 70 (1H, brs)	'H-NMR (CDCl ₃) & 2. 43(3H, s), 3. 99(2H, q, J=5. 3Hz), 6. 61(1H, s), 6. 97(1H, d, J=5. 9Hz), 7. 23(1H, s), 7. 53-7. 64(2H, m), 7. 83(1H, s), 7. 88(1H, s), 8. 07(1H, d, J=5. 9Hz), 8. 24-8. 28(1H, m), 8. 66(3H, brs), 11. 01(1H, brs)	¹ H-NMR (DMSO-d6) δ 8. 46 (3H, brs), 7. 95 (1H, d, J=6. 3Hz), 7. 55-7. 36 (2H, ω), 7. 28 (1H, dd, J=7. 9, 7. 6Hz), 7. 01 (1H, s), 6. 91 (1H, d, J=6. 3Hz), 4. 06 (2H, q, J=5. 3Hz), 3. 75 (2H, t, J=6. 6Hz), 2. 40 (3H, s), 1. 60-1. 51 (2H, m), 0. 76 (3H, t, J=7. 3Hz)	'H-NMR (DMSO-d6) & 1. 13 (3H, t, J=6. 9Hz), 2. 42 (3H, s), 3. 91 (2H, q, J=6. 9Hz), 4. 16 (2H, q, J=5. 0Hz), 6. 95 (1H, d, J=6. 3Hz), 7. 13 (1H, s), 7. 42 (1H, d, J=8. 6Hz), 7. 51 (1H, d, J=8. 6Hz), 7. 95 (1H, d, J=6. 3Hz), 8. 54 (3H, brs), 10. 96 (1H, brs)
	'H-NMR (CDC1 ₃) 6 2. 3 (1H, d, J=6. 3Hz), 7. (8. 6. 2. 0Hz), 7. 51 (1H), 10. 70 (1H, brs)	'H-NMR (CDC1 ₃) & 2, 43 IH, d, J=5, 9H2), 7, 23 s), 8, 07(IH, d, J=5, 9 brs)	¹ H-NMR (DMSO-d6) δ 8. 46 (3) 2H, ω), 7. 28 (1H, dd, 1=7. 9, 7 4. 06 (2H, q, 1=5. 3Hz), 3. 75 2H, ω), 0. 76 (3H, 1, 1=7. 3Hz)	"H-NMR (DMSO-d6) 8 1. 1. 6. 9Hz), 4. 16 (2H, q, J=5. (IH, d, J=8. 6Hz), 7. 51 (3H, brs), 10. 96 (IH, brs)
Product	Med H N N N N N N N N N N N N N N N N N N	H ₂ N ₁ N ₂ H ₃ N ₄	2HG B,N O'Fr	H ₃ N N N N 1 2 HCl OEs H
Reagent	Med. Me	BocHN As	Boc, N N N N N N N N N N N N N N N N N N N	Beerton O.E. H.
Example	203	504	506	521

Table 62

5

Ехав	Ехашр]е	Reagent	Product	Spectral data
2 2	2 2	BocHN OEt H	H ₂ N N N N N N N N N N N N N N N N N N N	'H-NWR (DMSO-d ₆) & 1. 10 (3H, 1, J=6. 9Hz), 2. 41 (3H, s), 2. 46 (3H, s), 3. 84 (2H, q, J=6. 9Hz), 3. 96-4. 19 (2H, m), 6. 91 (1H, d, J=6. 3Hz), 7. 04-7. 19 (2H, m), 7. 30 (1H, d, J=7. 9Hz), 7. 94 (1H, d, J=6. 3Hz), 8. 47 (3H, brs), 10. 95 (1H, brs)
8 4	4 1	Bocs N N N N	ZHCI H ₂ N N N	'H-NMR (DMSO-d ₆) & 10. 68(1H, brs), 8. 46(3H, brs), 7. 94(1H, d, J=5. 9 Hz), 7. 55-7. 36(2H, m), 7. 32-7. 22(1H, m), 7. 06(1H, s), 6. 90(1H, d, J=5. 9Hz), 4. 06(2H, s), 3. 67(3H, s), 2. 40(3H, s)
S.	ь 8	BocsN O'Pr	2HC Me	'H-NMR (DMSO-d ₆) δ 10. 66 (1H, brs), 8. 48 (3H, brs), 7. 95 (1H, d. J=6. 3Hz), 7. 50 (1H, d. J=8. 3Hz), 7. 44 (1H, d. J=7. 6Hz), 7. 27 (1H, dd. J=8. 3. 7. 6Hz), 7. 06 (1H, s), 6. 92 (1H, d. J=6. 3Hz), 4. 27-4. 12 (1H, m), 4. 07 (2H, q. J=5. 3Hz), 2. 41 (3H, s), 1. 07 (6H, d. J=5. 9Hz)

Example 3

Synthesis of 3-amino-2-(3-(di(t-butoxycarbonyl)aminomethyl)phenyl-amino)pyridine

[0059] A mixture of the compound (1.41 g) obtained in Example 1, 10% palladium-carbon (170 mg), methanol (60 ml) and ethyl acetate (30 ml) was stirred in a hydrogen atmosphere at room temperature for one day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 1.15 g of the titled compound (yield, 88%).

 1 H-NMR (CDCl₃) δ:1.45(18H, s), 3.40(2H, brs), 4.75(2H, s), 6.20(1H, brs), 6.77(1H, dd, J=7.6, 5.0Hz), 6.84-6.90(1H, m), 7.00(1H, dd, J=7.6, 1.3Hz), 7.13(1H, s), 7.19-7.23(2H, m), 7.82 (1H, dd, J=5.0, 1.3Hz)

[0060] The procedure of Example 3 was repeated using corresponding reagents to give the compounds shown in Table 63.

Table 63

Ехащріе	Reagent	Product	Spectral data
11	BosjN H NO3	Bocs,N NH,	'H-NMR (CDC1 ₃) 6 1. 45(18H, s), 3. 38(2H, brs), 4. 74(2H, s), 6. 35(1H, brs), 6. 83(1H, d, J=8. 9Hz), 6. 86(1H, d, J=7. 6Hz), 6. 98(1H, dd, J=8. 9, 2. 6Hz), 7. 10(1H, s), 7. 12(1H, d, J=7. 6Hz), 7. 20(1H, dd, J=7. 6, 7. 6Hz), 7. 79(1H, d, J=2. 6Hz)
15	Boc 1N N N	Boc ₃ N H ₂ N N ₁	'H-NWR (CDCI ₃) 6 1. 44(18H, s), 2. 22(3H, s), 3. 41(2H, brs), 4. 73(2H, s), 6. 11(1H, brs), 6. 72(1H, d, J=5. 0Hz), 6. 85(1H, d, J=7. 6Hz), 7. 01(1H, s), 7. 07(1H, d, J=7. 6Hz), 7. 20(1H, dd, J=7. 6Hz), 7. 72(1H, d, J=5. 0Hz)
19	Boc,1N DO,1N N OMe	Bor,N H, N OMe	'H-NMR (CDCI ₃) & 1. 44 (18H, s), 3. 88 (3H, s), 4. 76 (2H, s), 6. 15 (1H, d. 1=8. 3Hz), 6. 74 (1H, brs), 6. 86 (1H, d. 1=7. 8Hz), 7. 06 (1H, d. 1=8. 3Hz), 7. 23 (1H, dd, 1=7. 8, 7. 8Hz), 7. 36 (1H, s), 7. 49 (1H, d. 1=7. 8Hz)
445	BocHIV N N OME	Bechn M OMe	ROCHIN (CDC13) 6 7. 35 (1H, S), 7. 30-7. 23 (2H, M), 6. 92-6. 87 (1H, M), 6. 31 (1H, brs), 6. 21 (1H, S), 6. 05 (1H, S), 4. 81 (1H, brs), 4. 30 (2H, d, J=5. 6Hz) (1H, brs), 9. 2. 22 (3H, S), 1. 46 (9H, S)
455	Bocifiv N N N N N N N N N N N N N N N N N N N	BocHN N H Ma	'H-NMR (CDC1 ₃) & 1. 46(9H, s), 2. 17(3H, s), 3. 91(3H, s), 4. 31(2H, d, 1=5.6Hz), 4. 80(1H, br1), 6. 13(1H, s), 6. 18(1H, d, 1=7. 9Hz), 6. 89(1H, d, 1=7. 3Hz), 7. 21-7. 30(2H, m), 7. 49(1H, d, 1=7. 3Hz), 7. 62(1H, s)

Example 5

Synthesis of 3-methylamino-2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)pyridine

[0061] To a mixture of the compound (88.5 mg) obtained in Example 3, methyl iodide (15 μl) and dimethylformamide (2 ml), sodium hydride (content = 60%; 10 mg) was added and the resulting mixture was stirred at room temperature for 4 days. To the reaction mixture, ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 3) to give 19.3 mg of the titled compound (yield, 21%).

 1 H-NMR (CDCl₃) δ:1.44(18H, s), 2.85(3H, s), 3.48(1H, brs), 4.74(2H, s), 6.02(1H, s), 6.82-6.95(3H, m), 7.03(1H, s), 7.09(1H, d, J=8.0Hz), 7.20(1H, dd, J=8.0, 8.0Hz), 7.75 (1H, dd, J=4.3, 1.7Hz)

Example 6

15

30

35

Synthesis of 3-methylamino-2-(3-aminomethylphenylamino)pyridine

[0062] Using the compound obtained in Example 5 as a starting material, reaction was performed as in Example 2 and thereafter the liquid reaction mixture was concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, chloroform: methanol = 10 : 1) to give the titled compound quantitatively.

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>)
δ:1.69(2H, brs), 2.85(3H, s), 3.53(1H, brs), 3.81(2H, s), 6.08(1H, brs), 6.84-6.94(3H, m), 7.05(1H, d, J=7.6Hz),
7.12(1H, s), 7.22(1H, dd, J=7.6, 7.6Hz), 7.76 (1H, dd, J=4.6, 2.0Hz)
```

Example 7

Synthesis of 3-ethylamino-2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)pyridine

[0063] Using the compound obtained in Example 3 as a starting material and also using ethyl iodide as a reagent, the procedure of Example 5 was repeated to give the titled compound (yield, 54%).

```
<sup>1</sup>H-NMR (CDCl<sub>3</sub>)
δ:1.28(3H, t, J=7.3Hz), 1.45(18H, s), 3.15(2H, q, J=7.3Hz), 3.30(1H, brs), 4.74(2H, s), 6.05(1H, s), 6.82-6.96(3H, m), 7.07(1H, s), 7.12-7.18(1H, m), 7.18 (1H, dd, J=7.3, 7.3Hz), 7.75(1H, dd, J=4.6, 1.3Hz)
```

Example 29

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-6-methylamino-3-nitropyridine

[0064] A mixture of the compound (77.0 mg) obtained in Example 27, potassium carbonate (89 mg), methylamine hydrochloride (22.0 mg) and acetonitrile (2 ml) was stirred at 60°C for 6 h and the reaction mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the resulting residue. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 71.0 mg of the titled compound (yield, 93%).

```
^{1}\text{H-NMR} (CDCl<sub>3</sub>) \delta:1.43(18\text{H, s}),\ 3.03(3\text{H, d, J=4.3Hz}),\ 4.81(2\text{H, s}),\ 5.93(1\text{H, d, J=8.9Hz}),\ 6.98-7.80(5\text{H, m}),\ 8.20-8.42(1\text{H, m}),\ 10.81(1\text{H, brs})
```

55 [0065] The procedure of Example 29 was repeated using corresponding amine derivatives to give the compounds shown in Table 64.

Table 64

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10	Example	Amine derivative	Product	Spectral data
15	3 1	NH₁E¢HCI	Boc ₂ N NHE:	'H-NMR (CDCl ₃) δ 1. 32 (3H, t, J=6. 9Hz), 1. 43 (18H, s), 3. 38-3. 52 (2H, m), 4. 81 (2H, s), 5. 92 (1H, d, J=9. 2Hz), 6. 97-7. 78 (5H, m), 8. 26 (1H, d, J=9. 2Hz), 10. 79 (1H, brs)
20	3 3	NH ₂ *Pr.HCl	Boc ₂ N NH [*] Pr	'H-NMR (CDC1 ₃) & 1.00(3H, t, J=7.3Hz), 1.43(18H, s), 1.62-1.80(2H, m), 3.22-3.44(2H, m), 4.81(2H, s), 5.93(1H, d, J=6.5Hz), 6.95-7.83(5H, m), 8.20-8.37(1H, m), 10.80(1H, brs)
30	3 5	NHMe2.HCI	Boc ₃ N NMe ₂	'H-NMR (CDCl ₂) δ 1. 46 (18H, s), 3. 19 (6H, s), 4. 78 (2H, s), 6. 08 (1H, d, J=9. 6Hz), 7. 04 (1H, d, J=7. 6Hz), 7. 29 (1H, dd, J=7. 6, 7. 6Hz), 7. 58 (1H, s), 7. 59 (1H, d, J=7. 6Hz), 8. 28 (1H, d, J=9. 6 Hz), 10. 81 (1H, brs)

Example 37

Synthesis of 6-chloro-2-(3-(t-butoxycarbonylaminomethyl)phenylamino)nicotinic acid

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[0066] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (81 mg), 2,6-dichloronicotinic acid (90%, 53 mg), di-ipropylethylamine (64 mg) and 1,4-dioxane (1 ml) was heated under reflux for 3 days and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, methylene chloride:methanol = 20 : 1) to give 24 mg of the titled compound (yield, 25%).

¹H-NMR (DMSO-d₆) δ:1.44(9H, s), 4.14-4.26(2H, m), 6.72(1H, d, J=7.9Hz), 6.89(1H, d, J=7.6Hz), 7.09(1H, brt), 7.26(1H, dd, J=7.6, 7.6Hz), 7.51(1H, s), 7.71 (1H, d, J=7.6Hz), 8.22(1H, d, J=7.9Hz)

Example 39

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-6-methoxypyridine

[0067] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (50 mg), tetrakistriphenylphosphine palladium (18 mg), potassium carbonate (24 mg), 2-chloro-6-methoxypyridine (25 mg) and toluene (3 ml) was heated under reflux under nitrogen atmosphere for 16 h and, thereafter, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:hexane

= 1:4) to give 54.5 mg of the titled compound (yield, 82%).

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 1 H-NMR (CDCl₃) δ:1.45(18H, s), 3.91(3H, s), 4.77(2H, s), 6.19(1H, d, J=7.9Hz), 6.36(1H, brs), 6.39(1H, d, J=7.9Hz), 6.93(1H, d, J=6.9Hz) 7.23-7.30(3H, m), 7.39(1H, dd, J=7.9, 7.9Hz)

[0068] The procedure of Example 39 was repeated using corresponding aniline derivatives and corresponding halogenated derivatives to give the compounds shown in Tables 65 - 73 (under "Reaction conditions" in the tables: palladium Pd:(1) is tetrakistriphenylphosphine palladium, Pd:(2) is tris(dibenzylideneacetone)dipalladium, base:(1) is potassium t-butoxide, base:(2) is sodium t-butoxide, base:(3) is potassium carbonate; ligand:(1) is diphenylphosphino-ferrocene and ligand:(2) is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

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Table 65

Spectral data	'H-NLR & (CDC1 ₃) 1. 47(18H, s), 4. 78(2H, s), 6. 71(1H, brs), 6. 81(1H, dd, 1=7, 6, 4. 3Hz), 7. 02(1H, d, 1=7, 6Hz), 7. 29 (1H, dd, 1=7, 6, 7. 6Hz), 7. 43(1H, s), 7. 49(1H, d, 1=7, 6Hz), 7. 79(1H, d, 1=7, 6Hz), 8. 33(1H, d, 1=4, 3Hz)	1H-NMR (CDC1,) 6 1. 45 (18H, s), 3. 88 (3H, s), 3. 97 (3H, s). 4. 78 (2H, s), 6. 14 (1H, d, J=8. 8Hz), 6. 95 (1H, d, J=7. 6Hz). 7. 26 (1H, dd, J=7. 6, 7. 6Hz), 7. 59 (1H, d, J=7. 6Hz), 7. 66 (1H, s), 8. 10 (1H, d, J=8. 8Hz), 10. 42 (1H, brs)	¹ H-NMR (CDC1 ₃) 5 8. 27 (1H, d. J=8. 9Hz), 7. 45-7. 30 (3H, m), 7. 16-7. 06 (2H, m), 6. 32 (1H, d. J=8. 9Hz), 4. 79 (2H, s), 4. 09 (3H, s), 1. 46 (18H, s)	¹ H-NWR (CDC1 ₃) & 11.00(1H, brs), 8.46(1H, d, J=9.2Hz), 8.28(1H, d, J=8.3Hz), 7.28(1H, dd, J=8.3, 7.9Hz), 6.99 (1H, d, J=7.9Hz), 6.28(1H, d, J=9.2Hz), 4.95(2H, s), 3.95 (3H, s), 1.46(18H, s)
Reaction conditions	Pd : (1) base : (3)	Pd: (1) base: (3)	Pd: (1) base: (3)	Pd : (1) base : (3)
Product	Bossy ^N	Boc ₁ N OMe	Boc, N H N OMe base : (3)	Borgh C1
Halogenated derivative	N U	OM*	CI N OMe	JAO N D
Aniline derivative	Boc ₁ N NH ₂	Boc1N NH2	Boc ₂ N NH ₂	Boc ₁ N NH ₁
Example	4.	4 3	421	422

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Table 66

Spectral data	'H-NMR (CDC1 ₃) & 7. 38 (1H, brs), 7. 34-7. 27 (211, a), 6. 96 (1H d, 1=6. 6Hz), 6. 89 (1H, s), 6. 74 (1H, s), 6. 51 (1H, s), 4. 83 (1H, brs), 4. 31 (2H, d, 1=5. 6Hz), 3. 94 (3H, s), 3. 90 (3H, s), 1. 46 (9H, s)	'H-NWR (CDC1,) 6 8. 27 (114, d, 1=5. 6Hz), 7. 58 (111, s), 7. 55 (114, d, 1=7. 9Hz), 7. 10 (114, brs), 114, d, 1=7. 9Hz), 7. 10 (114, brs), 6. 94 (114, d, 1=7. 3Hz), 6. 61 (114, d, 1=5. 6Hz), 4. 83 (114, brs), 4. 32 (2H, d, 1=5. 6Hz), 2. 42 (3H, s), 1. 47 (9H, s)	'H-NMR (CDC1 ₃) & 1.39(31, 1, 1=6, 9H2), 1.47(18H s), 4.39(2H, q, 1=6, 9Hz), 4.79(2H, s), 6.20(1H, d, 1=8, 9Hz), 7.11(1H, d, 1=7, 6Hz), 7.32(1H, d), 1=7, 6, 7, 6Hz), 7.53(1H, s), 7.57(1H, d, 1=7, 6Hz), 8.41(1H, d, 1=8, 9Hz), 10.61(1H, brs)	'H-NWR (CDC1 ₁) 6 1. 46(18H, s), 3. 90 (3H, s), 4. 77(2H, s), 6. 22(1H, d, 1=8. 6Hz), 6. 73(1H, brs), 6. 99(1H, d, 1=7. 6Hz), 7. 26(1H, dd, 1=7. 6, 7. 6Hz), 7. 44(1H, s), 7. 49(1H, d, 1=7. 6Hz), 7. 66(1H, d, 1=8. 6Hz)
Sp	'H-NMR (CDC1 ₃)	'H-NNR (CDC1,) 6 8. 27 (1H, d, J=5, 6Hz), 7. 58 (IH, d, J=7. 9Hz), 7. 28 (1H, dd, J=7. 9, 7. 3Hz), 7. 6. 94 (1H, d, J=7. 3Hz), 6. 61 (1H, d, J=5, 6Hz), 4. 32 (2H, d, J=5, 6Hz), 2. 42 (3H, s), 1. 47 (9H, s)	⁴ H-NMR (CDC1 ₃) 6 1. 39 (31 2H, q. 1=6. 9Hz), 4. 79 (21 1H, d. 1=7. 6Hz), 7. 32 (11 7. 57 (1H, d. 1=7. 6Hz), 8.	'H-NWR (CDC1 ₃) & 1. 46(1 6. 22(1H, d, J=8. 6Hz), 6. 7 7. 26(1H, dd, J=7. 6, 7. 6H Hz), 7. 66(1H, d, J=8. 6Hz)
Reaction conditions	Pd: (2) base: (2) Jigand: (2)	Pd : (2) base: (1) ligand: (1)	Pd : (1) base: (3)	Pd : (1) base : (3)
Product	Bochin H N OMe Pd: (2)	Bochin A H	Boc,N C N N OE:	Boesh Ryc N OMe
alogenated derivative	N 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ž—Zz—Z	G N OER	P,C CONTONIC
Aniline derivative	Bochin Mily	Boc HIN NH1	Boc ₁ N NH ₁	Boc ₂ N NH ₂
Ехащрје	4 2 8	424	425	4 2 6

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Table 67

				
Spectral data	'H-NMR (CDC1 ₃) & 1. 46 (9H, s), 3. 83 (3H, s), 4. 32 (2H, d, J=5. 9 Hz), 4. 88 (1H, br1), 7. 03-7. 12 (3H, m), 7. 15 (1H, s), 7. 23 (1H, s), 7. 34 (1H, dd, J=7. 6, 7. 6Hz), 7. 63 (1H, d, J=3. 0Hz), 9. 30 (1H, brs)	'H-NUR(CDC1,) 6 1. 44(9H, s), 2. 09(3H, s), 4. 24(2H, d, 1=5. 9 Hz), 4. 80(H, br1), 6. 64(H, d, 1=7. 9Hz), 6. 66(H, s), 6. 87 (H, d, 1=7. 9, 7. 9Hz), 7. 19(H, dd, 1=7. 9, 7. 9Hz), 7. 19(H, dd, 1=7. 6, 7. 6Hz), 7. 43(H, d, 1=7. 6Hz), 7. 97(H, d, 1=7. 9Hz), 8. 24(H, brs)	'H-NJR (CDC1,) & 1. 37 (9H, s), 1. 63 (6H, s), 2. 24 (3H, s), 4. 99 (1H, brs), 6. 56 (1H, d, 1=5. 0Hz), 6. 70 (1H, s), 6. 74 (1H, brs), 7. 09 (1H, d, 1=7. 3Hz), 7. 20-7. 31 (3H, m), 8. 05 (1H, d, 1=5. 0Hz)	'H-NMR(CDCl ₃) 6 0.92(3H, 1, J=7, 3Hz), 1, 42(9H, S), 1, 66- 1, 82(2H, m), 2, 26(3H, S), 4, 43-4, 60(1H, m), 4, 77-4, 87(1H, m), 6, 52(1H, brs), 6, 58(1H, d, J=5, 0Hz), 6, 68(1H, s), 6, 94, (1H, d, J=6, 6Hz), 7, 17(1H, s), 7, 23-7, 32(2H, m), 8, 06(1H, d, J=5, 0Hz)
Reaction conditions	Pd: (1) base: (1)	Pd : (2) base : (1) ligand : (1)	Pd : (2) base: (1) ligand: (1)	Pd : (2) base: (1) ligand: (1)
Product	Bortin Opin Opin	BocHIN O'1N NE	BocHN Ne Me H	Bothin H N
Halogenated derivative	O,N OM.	O ₂ N	ž-\Z	ž – Ž
Aniline derivative	BocHin NH,	Boctin Mil.	Bochin Me Me	BaciliN NII,
Example	427	4 2 8	4 2 9	430

Table 6

Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
431	Boc, N NH,	B. N.	Bocs Me Me Me	Pd : (2) base: (1) fgand: (1)	'H-NWR (CDC1 ₃) & 1. 46 (18H, s), 2. 19 (3H, s), 2. 20 (3H, s), 4. 83 (2H, s), 6. 21 (1H, brs), 6. 27 (1H, s), 6. 52 (1H, d, 1=5. 0 Hz), 6. 60 (1H, d, 1=7. 6Hz), 6. 99 (1H, d, 1=7. 6Hz), 7. 18 (1H, dd, 1=7. 6, 7. 6Hz), 7. 24 (1H, s), 8. 02 (1H, d, 1=5. 0Hz)
4 3 2	BocHN NH1	Br N	Bochin H	Pd : (2) base: (1) ligand: (1)	'H-NAR (CDC1 ₃) & 1. 23 (3H, 1, 1=7. 3Hz), 1. 46 (9H, s), 2. 25 (3H, s), 2. 64 (2H, q, 1=7. 3Hz), 4. 33 (2H, q, 1=5. 3Hz), 4. 71 (1H, br1), 6. 44 (1H, br3), 6. 56 (1H, d, 1=5. 3Hz), 6. 64 (1H, s), 7. 14-7, 26 (3H, m), 8. 04 (1H, d, 1=5. 3Hz)
4 3 3	Eco NH2	Br N	BocHN H	Pd : (2) base: (1) ligand: (1)	'H-NMR(CDC1 ₃) 6 1. 44(3H, 1, 1=6. 9Hz), 1. 44(9H, s), 2. 22(3H, s), 4. 06(2H, q, 1=6. 9Hz), 4. 31(2H, d, 1=5. 6Hz), 5. 02(1H, br1), 6. 31(1H, brs), 6. 50(1H, s), 6. 51(1H, d, 1=5. 3Hz), 6. 83(1H, d, 1=8. 6Hz), 7. 16-7. 23(2H, m), 8. 01(1H, d, 1=5. 3 Hz)
434	BocHN NH1	B N	BocHN	Pd : (2) base: (1) ligand: (1)	'H-NWR (CDCI ₃) 6 1. 44 (9H, s). 2. 22 (3H, s). 2. 78-2. 86 (2H, m), 3. 25-3. 34 (2H, m), 4. 78 (1H, br1), 6. 54 (1H, d, 1=5. 3Hz), 6. 58 (1H, s), 6. 86 (1H, brs), 7. 01-7. 13 (1H, m), 7. 17-7. 28 (2H, m), 7. 66-7. 75 (1H, m), 8. 03 (1H, d, 1=5. 3Hz)

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5			'H-NUR (CDCI ₃) 6 1. 46(91, s). 2. 29(31, s). 4. 42(21, d, J=5. 6 Hz), 4. 96(11, br1), 6. 66(11, d, J=5. 012), 6. 69(11, s), 6. 81 (11, brs), 7. 02(11, d, J=7. 311z), 7. 23(11, dd, J=7. 3, 7. 31z), 7. 96(11, d, J=7. 31z), 8. 12(11, d, J=5. 011z)	'H-NWR (CDC1 ₃)' & 1.36(911, brs), 1.80-1, 95(111, m), 2.01-2.17(111, m), 2.45-2.60(41, m), 5.09(111, brs), 6.56(111, brs), 6.57(111, d, 1=5.31tz), 6.70(111, s), 7.11(11, d, 1=7.31tz), 7.22-7.31(311, m), 8.05(111, d, 1=5.31tz)	'H-NMR (CDC1 ₃) & 1. 44 (911, s), 2. 25 (311, s), 2. 72-2. 79 (2H, m), 3. 32-3. 42 (2H, m), 4. 56 (1H, br1), 6. 47 (1H, brs), 6. 56 (1H, d, J=4. 9112), 6. 65 (1H, s), 7. 10-7. 19 (2H, m), 7. 22-7. 30 (2H, m), 8. 05 (1H, d, J=4. 9112)	'H-NMR (CDC1,) & 1. 40 (3H, 1, 1=6. 9Hz), 1. 44 (18H, s), 2. 22 (3K, s), 3. 91 (2K, q, 1=6. 9Hz), 4. 89 (2H, s), 6. 60 (1H, q, 1=5. 0 Hz), 6. 68 (1H, s), 6. 77 (1H, s), 6. 79 (1H, q, 1=7. 9Hz), 7. 05 (1H, dd, 1=7. 9, 7. 9Hz), 7. 77 (1H, d, 1=7. 9Hz), 8. 09 (1H, d, 1=7. 5. 0Hz)
10		l data	. 2. 29 (314 s). 6. d. 1=5. 0Hz), 6. Hiz), 7. 23 (111, 2) (111, d. 1=5. 0Hz)	515), 1.80-1. (1.0), 5.09(1H, 6.70(1H, s), 7), 2, 25 (311, s), [1H, br1), 6, 47	J=6. 9Hz), I. 4 4. 89 (2H, s), 6 7), 6. 79 (1H, d, 1H, d, J=7. 9Hz
15		Spectral data	'H-NUR (CDC1 ₃) 6 1. 46(9H, s). 2. 29(3H, s). 4. 4. Hz), 4. 96(1H, br1), 6. 66(1H, d, 1=5. OHz), 6. 6 (1H, brs), 7. 02(1H, d, 1=7. 3Hz), 7. 23(1H, dd), 7. 96(1H, d, 1=7. 3Hz), 8. 12(1H, d, 1=5. OHz)	'H-NWR(CDC1,)' & 1.36(911, brs), 1.80-1.9 2.17(111, m), 2.45-2.60(41, m), 5.09(11, brs), 6.57(111, d, 1=5.3112), 6.70(111, s), 7.1112), 7.22-7.31(311, m), 8.05(111, d, 1=5.3112)	'H-NNR (CDC1 ₃) & 1. 44 (911, s d) 3. 32-3. 42 (211, m), 4. 56 (1H, d, J=4. 912), 6. 65 (11, s), 211, m), 8. 05 (111, d, J=4. 9112))
20			'H-NUR (CDC1, Hz), 4. 96 (IH, (IH, brs), 7.	'H-NMR(CDC] 2. 17(11f, m), brs), 6. 57(1 112), 7. 22-7.	'H-NMR (CDC1, m). 3. 32-3. 4 1H, d, J=4. 911: 211, m). 8. 05 (1	1H-NMR (CDC1 ₃ 31f, s), 3. 91 (Hz), 6. 68 (1H 11f, dd, J=7. 9 5. 011z)
25	69	Reaction conditions	Pd : (2) base: (1) ligand: (1)	Pd : (2) base: (1) ligand: (1)	Pd : (2) base: (1) ligand: (1)	Pd : (2) base : (1) ligand : (1)
30	Table	Product	NH NH	N N N N N N N N N N N N N N N N N N N	Me Me	M M M M M M M M M M M M M M M M M M M
35			Восни	BocHN	Bochin	BocsN
40	٠	Halogenated derivative	B. Z.	ÄX	ž-_r	B _r A
45		Aniline derivative	Boetin	BocHIN NIII,	Bortin MH,	Boc ₃ N NII ₃
50		Example	4 3 5	4 3 6 Bec	4 3 7 Box	4 3 8 Boo

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Table 70

Spectral data	'H-NMR (CDC13, 6 1. 44 (18H, s), 2. 26 (3H, s), 4. 88 (2H, s), 6. 45 (1H, brs), 6. 59 (1H, d, 1=5. 3Hz), 6. 62 (1H, s), 7. 08 (1H, s), 7. 25-7. 29 (2H, m), 8. 05 (1H, d, 1=5. 3Hz)	'H-NMR(CDC1 ₃) & 1. 45(18H, s), 3. 93(3H, s), 4. 78(2H, s), 6. 22(1H, d, J=8. 6Hz), 7. 00(1H, s), 7. 03(1H, d, J=7. 6Hz), 7. 29(1H, dd, J=7. 6, 7. 6Hz), 7. 46(1H, d, J=7. 6Hz), 7. 54(1H, d, J=8. 6Hz)	'H-NNR(CDC1 ₃) & 1. 47(9H, s), 4. 32(2H, d, J=5. 6Hz), 4. 86(1H, brs), 6. 71(1H, dd, J=7. 6, 5. 0Hz), 6. 97(1H, d, J=7. 6Hz), 6. 98(1H, s), 7. 30(1H, dd, J=7. 6, 7. 6Hz), 7. 52-7. 60(3H, m), 8. 12(1H, dd, J=5. 0, 1. 7Hz)	'H-NWR (CDC1 ₃) 6 1. 47 (911 s), 3. 89 (3H, s), 3. 98 (3H, s), 4. 35 (2H, d, 1=5. 4Hz), 4. 81 (1H, bf1), 6. 15 (1H, d, 1=8. 5Hz), 6. 96 (1H, d, 1=8. 3, 8. 3Hz), 7. 28 (1H, dd, 1=8. 3, 8. 3Hz), 7. 57 (1H, d, 1=8. 3Hz), 7. 77 (1H, s), 8. 11 (1H, d, 1=8. 5Hz), 10. 47 (1H, s)
Reaction conditions	Pd : (2) base: (1) ligand: (1)	Pd : (1) base : (3)	Pd: (2) base: (2) ligand: (1)	Pd: (1) base: (3)
Product	Boss ^M	Boc,N NC N OMe	BocHN	Boethy N N CO ₃ Me
alogenated derivative	ž – Ž	NC OME	∑z 5	O O We
Aniline derivative	Boc ₃ N NH ₂	Boc,N NH,	BocHN NH1	BocH/N NH,
Example	4 3 9	4 4 0	4 4 1	4 4 2

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Table 71

Example	Aniline	Halogenated derivative	Product	Reaction conditions	Spectral data
497	Bor, N	Br. N.	Ecr. M. H. M.	Pd : (2) base: (1) ligand: (1)	'H-NMR(CDC1 ₃) & 1. 46(18H, s), 2. 23(3H, s), 4. 76(2H, s), 6. 50(1H, brs), 6. 83(1H, d, J=6. 9Hz), 6. 93(1H, d, J=6. 9Hz), 7. 15-7. 36(4H, m), 8. 02(1H, s)
498	BocHN NH ₂	Me N	Boetty Me H	Pd : (2) base : (1) ligand : (1)	'H-NMR (CDC1 ₃) & 1. 46(914 s), 2. 24(311 s), 4. 30(2H d, 1=5. 6 Hz), 4. 83(1H, br1), 6. 13(1H, brs), 6. 72(1H, dd, 1=7. 3, 5. 0 Hz), 6. 91(1H, d, 1=7. 3Hz), 7. 27(1H, dd, 1=7. 6, 7. 6Hz), 7. 36(1H, d, 1=5. 0Hz), 7. 46(1H, s), 7. 48(1H, d, 1=7. 6Hz), 8. 11(1H, d, 1=5. 0Hz)
499	MeO NH,	M-K	Bor, N. C.	Pd : (2) base: (1) Ligand: (1)	'H-NNR (CDC1,) & 1. 43 (18H, s), 2. 20 (3H, s), 3. 82 (3H, s), 4. 81 (2H, s), 6. 27 (1H, brs), 6. 46 (1H, s), 6. 50 (1H, d, 1=5, 3 Hz), 6. 83 (1H, d, 1=8, 9Hz), 7. 00 (1H, d, 1=2, 3Hz), 7. 18 (1H, d, 1=8, 9, 2, 3Hz), 8. 00 (1H, d, 1=5, 3Hz)
200	Bortin Mil.	ž—Çz	Bodin Me	Pd : (2) base: (1) Igand: (1)	'H-NMR(CDC1,) 6 1. 44 (914 s), 2. 29 (314 s), 4. 11 (211, d, 1=6.6] Hz), 5. 72 (111, br1), 6. 42-6. 46 (111, m), 6. 60-6. 73 (311, m), -7. 24 (111, d, 1=8.61z), 7. 39-7. 45 (111, m), 7. 41 (111, s), 7. 50-7. 45 (111, m), 7. 41 (111, s), 7. 50-7. 45 (111, m), 7. 41 (111, s), 7. 50-7. 45 (111, d), 7. 72 (111, d, 1=1.31z), 7. 8. 09 (111, d, 1=5.31z)

Table 72

			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Spectral data	'H-NUR (CDC1,) & 8.09(111, d, 1=5.3112). 7.80(111, d, 1=7.9112). 7.05(111, dd, 1=7.9, 7.9112), 6.83-6.72(211, m), 6.66(111, s). 6.59(11, d, 1=5.312), 4.90(211, s), 3.78(211, t, 1=6.612), 2.28 (311, s), 1.90-1.75(211, m), 1.44(1811, s), 1.06(311, t, 1=7.3112)	'H-NUR (CDC1,) & 1, 45 (3H, 1, 1=6, 9Hz), 1, 45 (9H, s), 2, 29 (3H, s), 3, 94 (2H, q, 1=6, 9Hz), 4, 52 (1H, d, 1=5, 6Hz), 4, 94 (1H, brt), 6, 58 (1H, s), 6, 62 (1H, d, 1=5, 0Hz), 6, 74 (1H, brs), 7, 12 (1H, d, 1=8, 9Hz), 8, 10 (1H, d, 1=5, 0Hz)	'H-NMR (CDC1,) 6 1. 40 (3H, 1, 1=6. 9Hz), 1. 45 (9H, s), 2. 26 (3H, s), 2. 35 (3H, s), 3. 88 (2H, q, 1=6. 9Hz), 4. 39 (2H, d, 1=5. 0Hz), 7. 4. 76 (1H, brs), 6. 58 (1H, d, 1=5. 3Hz), 6. 61 (1H, s), 6. 93 (1H, d, 1=8. 2Hz), 7. 65 (1H, d, 1=8. 2Hz), 8. 07 (1H, d, 1=5. 3Hz)
Reaction conditions	Pd : (2) base: (1) ligand: (1)	Pd : (2) base: (1) llgand: (1)	Pd : (2) base: (1) ligand: (1)
Product	Me Pd : (2) Bocs N	Boctin Company (1) base: (1) base: (1)	Boelin OE H
Halogenated derivative	ž-Cz	ž-Cz	ž-Cz
Aniline derivative	Boc ₂ N NII ₁	BothN OE	Botin Mil,
Example	505	5 1 9	5 2 0

Table 73

Spectral data	'H-NMR(CDC1,) 6 8. 10 (11, d, 1=5. 3112), 7. 80 (11, d, 1=7. 3 Hz), 7. 06 (11, dd, 1=8. 6, 7. 3112), 6. 81 (11, s), 6. 77 (11, d. 1=8. 6Hz), 6. 69 (11, s), 6. 60 (11, d. 1=5. 3112), 4. 89 (21, s), 3. 75 (31, s), 2. 28 (31, s), 1. 45 (181, s)	'H-NMR (CDC1 ₃) 6 8.09 (111, d, J=5.3Hz), 7.74 (111, d, J=7.6Hz), 7.04 (111, dd, J=8.6, 7.6Hz), 6.80 (111, d, J=8.611z), 6.74 (111, s), 6.67 (111, s), 6.58 (111, d, J=5.3Hz), 4.88 (211, s), 4.19 -4.07 (111, m), 2.27 (311, s), 1.43 (1811, s), 1.29 (611, d, J=6.3 Hz)
Reaction conditions	Pd : (2) base: (1) ligand: (1)	Pd : (2) base: (1) ligand: (1)
Product	Boogh N N N	Bocsn OPP H
Halogenated derivative	Br N	B. A. A. R.
Aniline derivative	BacHN NH3	BociiN O'Pr
Example	540	542

Example 45

Synthesis of 2-(3-aminomethylphenylamino)-6-methoxynicotinic acid hydrochloride

[0069] A mixture of the compound (37 mg) obtained in Example 43, potassium hydroxide (96 mg), water (2 ml) and 1,4-dioxane (2 ml) was heated at 60°C for 2 h. The reaction mixture was cooled, then rendered acidic with 2 N HCl and subjected to extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was worked up as in Example 2 to give the titled compound quantitatively.

10 1H-NMR (DMSO-d₆)

8:3.95(3H, s), 4.01(2H, brs), 6.27(1H, d, J=8.6Hz), 7.14(1H, d, J=7.6Hz), 7.39(1H, dd, J=8.3, 7.6Hz), 7.71(1H, s), 7.90(1H, d, J=8.3Hz), 8.14(1H, d, J=8.6Hz), 8.30(3H, brs), 10.75 (1H, s), 13.06(1H, brs)

15 Example 52

Synthesis of 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine hydrochloride

[0070] A mixture of the compound (118 mg) obtained in Example 446, concentrated sulfuric acid (1 ml) and water (2 ml) was heated at 120°C for 4 h. The reaction mixture was put into ice water, adjusted to pH 8 with saturated sodium hydrogencarbonate and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and dried under reduced pressure. The resulting residue was dissolved in methanol (2 ml) and, after addition of a 1,4-dioxane solution (4 N, 0.5 ml) of hydrogen chloride at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was recrystallized from methanol-ethyl acetate to give 37.1 mg of the titled compound (61%).

¹H-NMR (DMSO-d₆)

δ:2.49(3H, s), 4.03(2H, q, J=5.6Hz), 6.90(1H, d, J=8.6Hz), 7.27(1H, d, J=7.9Hz), 7.42(1H, dd, J=7.9, 7.9Hz), 7.77 (1H, s), 7.86(1H, d, J=7.9Hz), 8.31(3H, brs), 8.45 (1H, d, J=8.6Hz), 10.09(1H, s)

Example 53

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Synthesis of 2-(3-aminomethylphenylamino)-6-ethyl-3-nitropyridine hydrochloride

95 [0071] Using the compound obtained in Example 447 as a starting material, the procedure of Example 52 was repeated to give the titled compound (yield, 85%).

¹H-NMR (DMSO-d₆)

δ:1.24(3H, t, J=7.3Hz), 2.79(2H, q, J=7.3Hz), 4.02(2H, q, J=5.0Hz), 6.92(1H, d, J=8.6Hz), 7.26(1H, d, J=7.6Hz), 7.43 (1H, dd, J=7.6, 7.6Hz), 7.75(1H, s), 7.90(1H, d, J=7.6Hz), 8.41(3H, brs), 8.48(1H, d, J=8.6Hz), 10.10(1H, s)

Example 443

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxy-isonicotinic acid

[0072] To a mixture of the compound (53.8 mg) obtained in Example 423 and methanol (3 ml), a 2N aqueous sodium hydroxide solution (1 ml) was added. The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. To the resulting residue, ethyl acetate was added and mixture was subjected to extraction with water. The aqueous layer was adjusted to pH 1 with 2N HCl and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 47.3 mg of the titled compound (yield, 90%).

1H-NMR(CDCl₃)

δ:7.49(1H, d, J=7.9Hz), 7.45(1H, s), 7.28(1H, dd, J=7.9, 7.3Hz), 6.98(1H, s), 6.93(1H, d, J=7.3Hz), 6.76(1H, s), 4.92(1H, brs), 4.31(2H, d, J=5.6Hz), 3.95(3H, s), 1.46(9H, s)

Example 444

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-hydroxymethyl-6-methoxypyridine

[0073] To a mixture of the compound (155.3 mg) obtained in Example 423, tetrahydrofuran (4 ml) and methanol (2 ml), lithium borohydride (13 mg) was added. The reaction mixture was stirred at room temperature for one week and, after addition of water, the mixture was concentrated under reduced pressure. Water was added to the resulting residue and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1:1) to give 86.1 mg of the titled compound (yield, 60%).

¹H-NMR(CDCl₃)

δ: 7.37(1H, s), 7.18-7.12(2H, m), 6.93-6.88(1H, m), 6.42(1H, s), 6.42(1H, s), 6.18(1H, s), 4.88(1H, brs), 4.59(2H, s), 4.29(2H, d, J=5.6Hz), 3.90(3H, s), 1.45(9H, s)

Example 446

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Synthesis of 2-(2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-3-nitropyridine-6-yl)malonic acid dimethyl ester

[0074] To a mixture of the compound (150 mg) obtained in Example 27, dimethyl malonate (50 mg) and dimethyl-formamide (3 ml), sodium hydride (content, 60%; 15 mg) was added. The reaction mixture was stirred at room temperature for 3 h and then ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 123 mg of the titled compound (yield, 68%).

¹H-NMR(CDCl₃)

8:1.47(18H, s), 3.76(6H, s), 4.81(2H, s), 4.91(1H, s), 6.95(1H, d, J=8.6Hz), 7.08(1H, d, J=7.9Hz), 7.32(1H, dd, J=7.9, 7.9Hz), 7.44(1H, s), 7.68(1H, d, J=7.9Hz), 8.54(1H, d, J=8.6Hz), 10.18(1H, brs)

[0075] The procedure of Example 446 was repeated using corresponding chlorinated derivatives forms and corresponding reagents to give the compounds listed in Table 74.

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Table 74

	s), 1, 85 (311, s), 8, 942), 7, 07 (111, (111, d, 1=2, 042), 17 (111, br s)	15 (211, d, J=5, 6Hz 2H, d, J=7, 6Hz), 12), 7, 60 (111, s),
Spectral data	'H-NMR (CDC ₃)	'H-NMR (CDC1,) 6 1. 47 (9H, s), 2. 53 (3H, s), 4. 35 (2H, d, J=5. 6Hz), 4. 85 (1H, br1), 6. 68 (1H, d, J=8. 9Hz), 7. 10 (2H, d, J=7. 6Hz), 7. 34 (1H, dd, J=7. 6, 7. 6Hz), 7. 52 (1H, d, J=7. 6Hz), 7. 60 (1H, s), 8. 27 (1H, d, J=8. 9Hz), 10. 45 (1H, brs)
Product	Bec,N CCO,EU,	1.H BocHN
Reagent	CH,CH (CO,Et),	MeSH
Example Chlorinated derivative	Bocs, N C H	BocHN N CO
Example	7 4 4 7	4 4 8

Example 449

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-methylpyridine

[0076] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)bromobenzene (260 mg), tris(dibenzylideneacetone)dipalladium (42 mg), diphenylphosphinoferrocene (50 mg), potassium t-butoxide (102 mg), 2-amino-4-methylpyridine (108 mg) and toluene (10 ml) was heated under a nitrogen atmosphere at 80°C for 22 h. Ethyl acetate and water were added to the reaction mixture. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 1) to give 29.2 mg of the titled compound (yield, 10%).

¹H-NMR(CDCl₃)

δ:1.46(9H, s), 2.26(3H, s), 4.30(2H, d, J=5.9Hz), 4.90(1H, brt), 6.59(1H, d, J=5.0Hz), 6.60(1H, s), 6.68(1H, s), 6.94(1H, d, J=6.3Hz), 7.21-7.31(3H, m), 8.06(1H, d, J=5.0Hz)

[0077] The procedure of Example 449 was repeated using corresponding amine derivatives to give the compounds listed in Table 75.

Table 75

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Example	Amine derivative	Product	Spectral data
450	Me H ₂ N N Me	BocHN N N Me	¹ H-NMR (CDCl ₃) δ 1. 46 (9H, s), 2. 22 (3 H, s), 2. 40 (3H, s), 4. 30 (2H, d, J=5. 6. Hz), 4. 83 (1H, brt), 6. 43 (1H, brs), 6. 47 (1H, s), 6. 53 (1H, s), 6. 93 (1H, d, J=7. 3Hz), 7. 19-7. 29 (3H, m)
451	H ₂ N N	BOCHIN N N	¹ H-NMR (CDC1 ₂) & 1. 21 (3H, t, J=7. 6Hz), 1. 46 (9H, s), 2. 56 (2H, q, J=7. 6Hz), 4. 30 (2H, d, J=5. 6Hz), 4. 83 (1H, brt), 6. 54 (1H, brs), 6. 61 (1H, d, J=5. 0Hz), 6. 69 (1H, s), 6. 91-6. 95 (1H, m), 7. 18-7. 31 (3H, m), 8. 09 (1H, d, J=5. 0Hz)

Example 452

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxynicotinic acid

[0078] Using the compound obtained in Example 442 as a starting material, the procedure of Example 45 was repeated to give the titled compound (yield, 92%).

¹H-NMR(CDCl₃-CD₃OD)

δ:1.46(9H, s), 3.99(3H, s), 4.30(2H, s), 6.16(1H, d, J=8.6Hz), 6.94(1H, d, J=7.8Hz), 7.28(1H, dd, J=7.8, 7.8Hz), 7.58(1H, d, J=7.8Hz), 7.73(1H, s), 8.16(1H, d, J=8.6Hz)

5 Example 453

Synthesis of 2-(3-t-butoxycarbonylaminomethyl)phenylamino)-6-methoxynicotinamide

[0079] To a mixture of the compound (44 mg) obtained in Example 452, triethylamine (18 mg) and tetrahydrofuran (2 ml), ethyl chlorocarbonate (14.3 mg) was added and the resulting mixture was stirred at room temperature for 15 min. Ammonia gas was blown through the reaction mixture at room temperature and after stirring at room temperature for 5 min, the mixture was concentrated under reduced pressure. To the resulting residue, a saturated aqueous sodium hydrogen-carbonate solution was added and the mixture was subjected to extraction with methylene chloride. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by preparative thin-layer chromatography (eluent, methanol:methylene chloride = 1 : 20) to give 10 mg of the titled compound (yield, 11%).

1H-NMR(DMSO-d₆)

8: 1.39 (9H, s), 3.92(3H, s), 4.12(2H, d, J=5.9Hz), 6.20(1H, d, J=8.6Hz), 6.85(1H, d, J=7.6Hz), 7.24(1H, dd, J=7.6, 7.6Hz), 7.32-7.40(2H, m), 7.51(1H, d, J=7.6Hz), 7.61(1H, s), 8.01(1H, brs), 8.10(1H, d, J=8.6Hz)

Example 454

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Synthesis of 2-(3-(1-butoxycarbonylaminomethyl)phenylamino)-3-hydroxymethyl-6-methoxypyridine

[0080] To a mixture of the compound (300 mg) obtained in Example 452, triethylamine (101 mg) and tetrahydrofuran (8 ml), a tetrahydrofuran solution (1 ml) of ethyl chlorocarbonate (109 mg) was added under ice cooling and the resulting mixture was stirred at 0°C for 15 min. The reaction mixture was filtered and a tetrahydrofuran solution (2 M, 0.8 ml) of lithium borohydride was added to the filtrate under ice cooling. The reaction mixture was stirred at 0°C for 30 min and thereafter a 1 N aqueous sodium hydroxide solution was added under ice cooling. Further, the reaction mixture was stirred at 0°C for 5 min and then ether and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:methylene chloride = 1 : 10) to give 199 mg of the titled compound (yield, 69%).

¹H-NMR(CDCl₃)

δ: 1.46(9H, s), 3.93(3H, s), 4.31(2H, d, J=5.6Hz), 4.67(2H, d, J=5.6Hz), 4.79(1H, brt), 6.15(1H, d, J=7.9Hz), 6.89(1H, d, J=7.6Hz), 7.21-7.31(3H, m), 7.48(1H, d, J=7.6Hz), 7.64(1H, brs), 7.70(1H, brs)

40 Example 456

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxypyridine-3-carboaldehyde

[0081] A mixture of the compound (24 mg) obtained in Example 454, manganese tetraoxide (40 mg) and benzene (8 ml) was stirred at room temperature for 2 days.

[0082] The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:methylene chloride = 1 : 20) to give 14 mg of the titled compound (yield, 59%).

¹H-NMR(CDCl₃)

δ:1.47(9H, s), 4.01(3H, s), 4.33(2H, d, J=5.6Hz), 4.82(1H, brt), 6.24(1H, d, J=8.3Hz), 7.00(1H, d, J=7.6Hz), 7.30(1H, dd, J=7.6, 7.6Hz), 7.61(1H, d, J=7.6Hz), 7.71(1H, d, J=8.3Hz), 7.72(1H, s), 9.67(1H, s), 10.95(1H, s)

Example 472

Synthesis of 2-(3-aminomethylphenylamino)-4-hydroxymethyl-6-methoxypyridine dihydrochloride

[0083] To a mixture of the compound (109.5 mg) obtained in Example 423, tetrahydrofuran (4 ml) and methanol (1

ml), lithium borohydride (19 mg) was added. The reaction mixture was stirred at room temperature for 44 h and after addition of 2 N HCI, the resulting mixture was concentrated under reduced pressure. The resulting residue was subjected to basic silica gel column chromatography (eluent, methanol:methylene chloride = 1 : 19). To a mixture of the purified product and methanol (3 ml), a 1,4-dioxane solution (4 N, 0.3 ml) of hydrogen chloride was added and the resulting mixture was concentrated under reduced pressure. The resulting residue was recrystallised from methanolethyl acetate to give 48 mg of the titled compound (yield, 58%).

```
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>)
δ:9.18(1H, brs), 8.39(3H, brs), 7.78(1H, s), 7.61(1H, d, J=7.9Hz), 7.29(1H, dd, J=7.9, 7.3Hz), 7.08(1H, brs), 7.02(1H, d, J=7.3Hz), 6.47(1H, s), 6.11(1H, s), 4.42(2H, s), 3.94(2H, q, J=5.6Hz), 3.87(3H, s)
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Example 507

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Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-5-methylthiazole

[0084] To a mixture of propionaldehyde (72 μ l), chloroform (1 ml) and 1,4-dioxane (1 ml), bromine (52 μ l) was added. The reaction mixture was stirred at room temperature for 30 min and then N-(3-(t-butoxycarbonylaminomethyl)phenyl)thiourea (262 mg), acetone (2 ml) and triethylamine (0.14 ml) were added. The reaction mixture was heated under reflux for 3.5 h and concentrated under reduced pressure. To the resulting residue, water was added and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, methylene chloride:methanol = 99 : 1) to give 79.2 mg of the titled compound (yield, 27%).

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>)
δ:7.30-7.22(4H, m), 7.17(1H, d, J=7.6Hz), 6.91(1H, d, J=1.0Hz), 4.94(1H, brs), 4.30(2H, d, J=5.6Hz), 2.34(3H, d, J=1.0Hz), 1.47(9H, s)
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Example 508

Synthesis of 2-(3-aminomethylphenylamino)-5-methylthiazole

[0085] A mixture of the compound (73 mg) obtained in Example 507 and trifluoroacetic acid (5 ml) was stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, methylene chloride methanol = 95 : 5) to give 34.5 mg of the titled compound (yield, 67%).

```
^{1}H-NMR(CDCl<sub>3</sub>) \delta:7.32-7.28(3H, m), 7.19(1H, d, J=7.3Hz), 6.97(1H, d, J=7.3Hz), 6.92(1H, d, J=1.0Hz), 3.87(2H, s), 2.35(3H, d, J=1.0Hz), 1.76(2H, brs)
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Example 509

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-methylthiazole

Example 511

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-5-methyloxazole

- [0086] To a mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (200 mg), dimethylaminopyridine (166 mg) and methylene chloride (10 ml), thiophosgene (45 µl) was added under ice cooling and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 3) to give N-(3-(di-(t-butoxycarbonyl)aminomethyl)phenyl)isothiocyanate.
- [0087] A mixture of the thus obtained compound (193 mg), 1-azido-propane-2-one (81 mg), triphenylphosphine (217 mg) and methylene chloride (5 ml) was stirred at room temperature for 15 h and then oxalic acid (115 mg) was added at room temperature. The reaction mixture was heated under stirring at 60°C for 30 min and concentrated under reduced pressure. To the resulting residue, ethyl acetate and a 2 N aqueous sodium hydroxide solution were added.

The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 10) to give 78 mg of the titled compound (yield, 33%).

 1 H-NMR(CDCl₃) δ:1.45(18H, s), 2.25(3H, d, J=1.0Hz), 4.77(2H, s), 6.51(1H, d, J=1.0Hz), 6.91(1H, d, J=7.6Hz), 7.15(1H, brs), 7.22-7.26(1H, m), 7.25(1H, dd, J=7.6, 7.6Hz), 7.40(1H, d, J=7.6Hz)

[0088] The procedure of Example 511 was repeated using corresponding reagents to give the compounds shown in Table 76.

Table 76

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	Example	Aniline derivative	Product	Spectral data
25			Me	'H-NMR (CDCl ₃) δ 1. 43 (18H, s), 1. 46 (3H, t, J=6. 9Hz), 2. 27 (3H, d, J=1. 0Hz),
	512	Boc ₃ N NH ₃	Boczin OEI H	3. 93 (2H, q, J=6. 9Hz), 4. 88 (2H, s), 6. 52 (1H, d, J=1. 0Hz), 6. 77 (1H, d, J=
30				7. 6Hz), 7. 08 (1H, dd, J=7. 6, 7. 6Hz), 7. 19 (1H, s), 8. 02 (1H, d, J=7. 6Hz)
35	513	Boc ₃ N NH ₃	Boc ₃ N Me	H-NMR (CDC1 ₃) δ 1. 44 (18H, s), 2. 21 (3H, s), 2. 24 (3H, s), 4. 82 (2H, s), 6. 48 (1H, s), 6. 88 (1H, d, J=7. 9Hz), 7. 19 (1H, dd, J=7. 9Hz), 7. 77 (1H, d, J=7. 9Hz)
40				'H-NMR(CDCl ₃) δ 1. 44(18H, s), 2. 23(
45	514	MeO NH ₂	MeO Me Boc ₂ N N	3H, s), 3. 79 (3H, s), 4. 80 (2H, s), 6. 46 (1H, s), 6. 81 (1H, d, J=8. 9Hz), 6. 97 (1H, d, J=2. 3Hz), 7. 45 (1H, dd, J=8. 9, 2. 3Hz)

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Example 515

Synthesis of 2-(3-aminomethyl)phenylamino)-5-methyloxazole trifluoroacetic acid salt

[0089] A mixture of the compound (292 mg) obtained in Example 511 and trifluoroacetic acid (2 ml) was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was recrystallised from ethanol/ethyl acetate/n-hexane to give 119 mg of the titled compound (38%).

1H-NMR(DMSO-d₆)

Example

Reagent

 δ :2.24(3H, s), 3.98(2H, q, J=5.6Hz), 6.59(1H, s), 7.00(1H, d, J=7.3Hz), 7.32(1H, dd, J=7.3, 7.3Hz), 7.53(1H, d, J=7.3Hz), 7.67(1H, s), 8.16(3H, brs), 10.08(1H, s)

5 [0090] The procedure of Example 515 was repeated using corresponding reagents to give the compounds listed in Table 77.

Product

Spectral data

Table 77

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		·	'H-NMR (DMSO-d _a) δ 1. 37 (3H, t, J=6. 9
			Hz), 2. 24(3H, s), 3. 89(2H, q, J=6. 9
516	o de	, o-M*	Hz), 4. 05 (2H, q, J=5. 6Hz), 6. 63 (1H,
	Boc ₃ N N	H ₂ N N	s), 7. 08(1H, d, J=7. 9Hz), 7. 15(1H,
	OEt	CF,CO,H	dd, J=7. 9, 7. 9Hz), 8. 13(1H, d, J=7. 9
			Hz), 8, 18 (3H, brs), 9, 33 (1H, brs)
			'H-NMR (DMSO-d ₆) δ 2. 22 (3H, s), 2. 23
			(3H, s), 4. 05 (2H, q, J=5. 6Hz), 6. 60 (
517	o Ma	o Me	1H, s), 7. 12(1H, d, J=7. 9Hz), 7. 24(
	Boc3N N	H ₂ N N	1H, dd, J=7. 9, 7. 9Hz), 7. 75 (1H, d, J=
	Me —	CF ₃ CO ₃ H	7. 9Hz), 8. 18(3H, brs), 9. 40(1H, brs
)
			'H-NMR (DMS0-d ₆) & 2. 22 (3H, s), 3. 80
	MeO Me	MeO Me	(3H, s), 3. 94(2H, q, J=5. 6Hz), 6. 55(
5 1 8	Boc ₃ N N	H ₃ N N	1H, s), 7. 02(1H, d, J=8. 9Hz), 7. 54(
	_	СРуСОуН "	1H, dd, J=8. 9, 2. 3Hz), 7. 59(1H, d, J=
			2. 3Hz), 8. 00 (3H, brs), 9. 87 (1H, s)

Example 523

Synthesis of 2-(3-aminomethylphenylamino)-3,5-dinitropyridine

[0091] A mixture of 3-aminobenzylamine (696 mg), dimethylaminopyridine (674 mg), 3-nitrophenyloxycarbonyl-Wang resin (2.85 g; Tetrahedron Lett., Vol, 37, 937 (1996)) and tetrahydrofuran (60 ml) was stirred at room temperature for 24 h and then filtered. The resulting resin was washed sequentially with dimethylformamide, water, methanol and methylene chloride and then dried under reduced pressure to give 3-aminobenzylaminocarbonyl-Wang resin.

[0092] A mixture of the thus obtained resin (100 mg, 0.071 mol), potassium carbonate (100 mg), 2-chloro-3,5-dinitropyridine (72 mg), palladium (II) acetate (16 mg), diphenylphosphinoferrocene (79 mg) and acetonitrile (9 ml) was stirred under a nitrogen atmosphere at 80°C and then filtered. The resulting resin was washed sequentially with dimethylfor-

mamide, water, methanol and methylene chloride, dried under reduced pressure and, after adding trifluoroacetic acid, the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. To the resulting residue, water and ethyl acetate were added. The aqueous layer was washed with ethyl acetate and concentrated under reduced pressure. The resulting residue was purified with Sep-PaK^R Plus C18 Cartridges (Waters) to give 1.7 mg of the titled compound (8%).

 1 H-NMR(CD₃OD) δ :4.16(2H, s), 7.35(1H, d, J=7.9Hz), 7.53(1H, dd, J=7.9, 7.9Hz), 7.75(1H, d, J=7.9Hz), 7.80(1H, s), 9.25(1H, d, J=2.4Hz), 9.30(1H, d, J=2.4Hz)

[0093] The procedure of Example 523 was repeated using corresponding chlorinated derivatives to give the compounds listed in Tables 78 - 80.

Table 78

	1)	Pd(OAc) ₂
	Marriantad	DPPF
Q O O NH	chlorinated derivatives	K ₂ CO ₃ toluene,N ₂
	+ -	TFA product
NO3	2	114

Example	Chlorinated derivative	Product	Spectral data
5 2 4	Me NC N Me	H ₂ N NC Me	¹ H-NMR (CD ₂ OD) 2. 35 (3H, s), 2. 44 (3H, s). 4. 13 (2H, s), 6. 78 (1H, s), 7. 19-7. 50 (3H, m), 7. 72 (1H, d, J=2. OHz)
5 2 5		H ₂ N CN	¹ H-NMR (CD ₃ OD) 4. 18 (2H, s), 7. 33-7. 46 (4 H, m), 7. 51 (1H, d, J=7. 6Hz), 7. 64 (1H, dd, J=7. 6, 7. 6Hz), 8. 45 (1H, d, J=5. OHz)
5 2 6	CI N	H ₂ N N CN	'H-NMR (CD ₃ OD) 4. 17 (2H, s), 7. 29 (1H, d, J= 8. 7Hz), 7. 34 (1H, d, J=7. 6Hz), 7. 39 (1H, s), 7. 53 (1H, d, J=7. 6Hz), 7. 64 (1H, dd, J= 7. 6, 7. 6Hz), 8. 04 (1H, dd, J=8. 7, 2. 0Hz), 8. 61 (1H, d, J=2. 0Hz)
5 2 7	CO ₂ E2	H ₁ N NC CO ₁ Et	¹ H-NMR (CD ₃ OD) 1. 47 (3H, t, J=7. 3Hz), 2. 56 (3H, s), 4. 14 (2H, s), 4. 48 (2H, q, J=7. 3 Hz), 7. 27 (1H, d, J=7. 9Hz), 7. 30 (1H, s), 7. 46 (1H, dd, J=7. 9, 7. 9Hz), 7. 74 (1H, s), 7. 75 (1H, d, J=7. 9Hz)
5 2 8	CO3H	H ₂ N N CO ₂ H	¹ H-NMR (CD ₂ OD) 4. 12 (2H, s), 7. 02-7. 12 (2H, m), 7. 26 (1H, d, J=5. 2Hz), 7. 37-7. 42 (2H, m), 7. 81 (1H, s), 8. 18 (1H, d, J=5. 2 Hz)

Table 79

5	Example	Chlorinated derivative	Product	Spectral data
10	5 2 9	CI N CO2H	H ₂ N CO ₂ H	'H-NMR (CD ₂ OD) 4. 15 (2H, s), 6. 87 (1H, d, J= 8. 7Hz), 7. 14 (1H, d, J=7. 4Hz), 7. 43 (1H, dd, J=7. 4, 6. 9Hz), 7. 53 (1H, d, J=6. 9Hz), 7. 98 (1H, s), 8. 11 (1H, J=8. 7, 2. 1Hz), 8. 81 (1H, d, J=2. 1Hz)
20	530	CI N CO'H	H ₂ N CO ₂ H	¹ H-NMR (CD ₂ OD) 4. 16 (2H, s), 7. 22 (1H, d, J=7. 9Hz), 7. 47 (1H, dd, J=7. 9, 7. 9Hz), 7. 65 (1H, d, J=7. 9Hz), 7. 92 (1H, s), 8. 22 (1H, d, J=2. OHz), 8. 69 (1H, d, J=2. OHz)
25	5 3 1	0 N Me	H ₂ N N M ₀	'H-NMR (CD ₃ OD) 2. 49 (3H, s), 4. 12 (2H, s), 7. 05 (1H, d. J=6. 2Hz), 7. 15 (1H, s), 7. 25 (1H, s), 7. 38-7. 42 (2H, m), 7. 72 (1H, s)
35	532	CO.H	H ₃ N CO ₃ H	'H-NMR (CD ₃ OD) 4. 14 (2H, s), 6. 82 (1H, d, J= 8. 9Hz), 7. 10 (1H, d, J=6. 6Hz), 7. 41-7. 45 (2H, m), 8. 02 (1H, s), 8. 11 (1H, dd, J=8. 9; 2. OHz), 8. 78 (1H, d, J=2. OHz)
40	533	H ₃ NOC Me	H ₂ N N CONH ₂	'H-NMR (CD ₃ OD) 2. 50 (3H, s), 4. 12 (2H, s), 6. 84 (1H, d, J=7. 6Hz), 7. 20 (1H, d, J=7. 0Hz), 7. 40 (1H, dd, J=7. 0, 7. 0Hz), 7. 74-7. 80 (2H, m), 7. 87 (1H, d, J=7. 6Hz)
45	534	H ₃ NOC CI	H ₂ N N CONH ₃	'H-NMR (CD ₃ OD) 4. 15 (2H, s), 7. 21 (1H, d. J= 7. 6Hz), 7. 46 (1H, dd, J=7. 6, 7. 6Hz), 7. 61 (1H, d, J=7. 6Hz), 7. 75 (1H, s), 8. 11 (1H, d, J=2. 6Hz), 8. 35 (1H, d. J=2. 6Hz)

Table 80

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	Example	Chlorinated derivative	Product	Spectral data
10	5 3 5	CI N OMe	CONH ₂ H ₂ N N OMe	H-NMR (CD ₂ OD) 4. 00 (3H, s), 4. 12 (2H, s), 6. 58 (1H, d, J=1. OHz), 6. 81 (1H, d, J=1. 0 Hz), 7. 09 (1H, d, J=6. 9Hz), 7. 37-7. 43 (1H, m), 7. 53 (1H, d, J=6. 9Hz), 7. 83 (1H, s)
20	5 3 6	H ₃ NOC	H ₂ N N CONH ₂	'H-NMR (CD ₃ OD) 4. 15 (2H, s), 6. 83-6. 89 (1H, m), 6. 96 (1H, dd, J=7. 6, 3. 9Hz), 7. 21 (1H, d, J=7. 6Hz), 7. 46 (1H, dd, J=7. 6, 7. 6 Hz), 7. 62 (1H, d, J=7. 6Hz), 7. 76 (1H, s), 8. 02 (1H, dd, J=7. 6, 1. 6Hz), 8. 37 (1H, dd, J=3. 9, 1. 6Hz)
30	537	CI N Br	H ₂ N N N N N N N N N N N N N N N N N N N	'H-NNR (CD ₃ OD) 4. 12 (2H, s), 6. 82 (1H, d, J=9. 0Hz), 7. 08 (1H, d, J=7. 6Hz), 7. 38 (1H, dd, J=7. 6, 7. 6Hz), 7. 50 (1H, d, J=7. 6Hz), 7. 71 (1H, dd, J=9. 0, 2. 3Hz), 7. 90 (1H, s), 8. 22 (1H, d, J=2. 3Hz)
<i>35</i>	5 3 8		H ₂ N C N C	'H-NMR (CD ₂ OD) 4. 13 (2H, s), 7. 16 (1H, d, J= 7. 6Hz), 7. 43 (1H, dd, J=7. 6. 7. 6Hz), 7. 64 (1H, d, J=7. 6Hz), 7. 84 (1H, s), 7. 87 (1H, d, J=2. 3Hz), 8. 10 (1H, d, J=2. 3Hz)
45	5 3 9	CI N Me	H ₂ N N Me	'H-NMR (CD ₃ OD) 2. 48 (3H, s), 4. 13 (2H, s), 6. 72-6. 80 (2H, m), 7. 35-7. 42 (1H, m), 7. 44 (1H, s), 7. 51-7. 60 (1H, m), 7. 68 (1H, dd, J=7. 9, 7. 9Hz), 7. 74 (1H, s)

[0094] Several compounds used in the reactions described above are novel and the methods of synthesizing these compounds are described below as Examples 25e, 417e, 500b, 519e, 520d, 538e and 542a.

Example 25e

Synthesis of 2-(5-amino-2-ethylphenyl)-2-(t-butoxycarbonylamino)indane

5 [Example 25a]

Synthesis of 3-cyanomethyl-4-ethylnitrobenzene

[0095] To a mixture of 3-chloromethyl-4-ethylnitrobenzene (4.0 g) and dimethyl sulfoxide (50 ml), sodium cyanide (982 mg) was added. The reaction mixture was stirred at room temperature for 3 h and then ethyl acetate, n-hexane and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound quantitatively.

¹H-NMR(CDCl₃)

 δ :1.33(3H, t, J=7.6Hz), 2.78(2H, q, J=7.6Hz), 3.80(2H, s), 7.44(1H, d, J=8.6Hz), 8.18(1H, dd, J=8.6, 2.3Hz), 8.35(1H, d, J=2.3Hz)

[Example 25b]

20 Synthesis of 2-cyano-2-(2-ethyl-5-nitrophenyl)indane

[0096] To a mixture of the compound (3.0 g) obtained in Example 25a, α,α'-dichloro-o-xylene (4.15 g) and dimethyl sulfoxide (200 ml), potassium t-butoxide (3.55 g) was added and after stirring the resulting mixture at room temperature for 3h, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound (1.36 g) (yield, 29%).

¹H-NMR(CDCl₃)

 δ :1.45(3H, t, J=7.6Hz), 3.11(2H, q, J=7.6Hz), 3.61(2H, d, J=15.5Hz), 3.91(2H, d, J=15.5Hz), 7.25-7.33(4H, m), 7.53(1H, d, J=9.2Hz), 8.12-8.16(2H, m)

[Example 25c]

Synthesis of 2-(2-ethyl-5-nitrophenyl)-2-indaneamide

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[0097] To a mixture of the compound (1.16 g) obtained in Example 25b and acetic acid (10 ml), water (2 ml) and concentrated sulfuric acid (20 ml) were added sequentially. The reaction mixture was heated under reflux for 13 h, cooled, put into ice water and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound (870 mg) (yield, 71%).

¹H-NMR(CDCl₃)

8:1.35(3H, t, J=7.6Hz), 2.82(2H, q, J=7.6Hz), 3.36(2H, d, J=15.9Hz), 3.95(2H, d, J=15.9Hz), 5.13(1H, brs), 5.43(1H, brs), 7.15-7.25(4H, m), 7.49(1H, d, J=8.3Hz), 8.08(1H, dd, J=8.3, 2.3Hz), 8.17(1H, d, J=2.3Hz)

[Example 25d]

Synthesis of 2-(t-butoxycarbonylamino)-2-(2-ethyl-5-nitrophenyl)indane

[0098] To a mixture of the compound (815 mg) obtained in Example 25c and t-butanol (12 ml), lead tetracetate (1.40 g) was added. The reaction mixture was heated under reflux for 3 h, cooled and, after adding water, subjected to extraction with ethyl acetate-ethylene glycol. The organic layer was washed with water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, chloroform) to give the titled compound (620 mg) (yield, 62%).

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 1 H-NMR(CDCl₃) δ:1.30(3H, t, J=7.6Hz), 1.31(9H, s), 2.93(2H, q, J=7.6Hz), 3.55(2H, d, J=15.9Hz), 3.63(2H, d, J=15.9Hz), 5.18(1H, s), 7.20-7.29(4H, m), 7.40(1H, d, J=8.6Hz), 8.05(1H, dd, J=8.6, 2.3Hz), 8.32(2H, d, J=2.3Hz)

[Example 25e]

Synthesis of 2-(5-amino-2-ethylphenyl)-2-(t-butoxycarbonylamino)indane

5 [0099] Using the compound obtained in Example 25d as a starting material, the procedure of Example 3 was repeated to give the titled compound (yield, 97%).

¹H-NMR(CDCl₃) δ:1.23(3H, t, J=7.6Hz), 1.30(9H, s), 2.74(2H, q, J=7.6Hz), 3.48-3.67(6H, m), 5.02(1H, s), 6.56(1H, dd, J=8.3, 2.3Hz), 6.74(1H, d, J=2.3Hz), 7.03(1H, d, J=8.3Hz), 7.15-7.24(4H, m)

Example 417e

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Synthesis of N-(3-amino-2-ethoxyphenylmethyl)iminodicarboxylic acid di-t-butyl ester

[Example 417a]

Synthesis of 2-ethoxy-3-nitrobenzoic acid ethyl ester

20 [0100] To a mixture of 3-nitrosalicylic acid (5.0 g), ethyl iodide (11 ml) and dimethylformamide (200 ml), potassium carbonate (9.4 g) was added. The reaction mixture was stirred at 60°C for 4.5 h and, after adding water, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 1) to give 5.66 g of the titled compound (yield, 87%).

 $^{1}\text{H-NMR}(\text{CDCl}_{3}) \\ \delta:8.01(1\text{H}, \ dd, \ J=7.9, \ 1.7\text{Hz}), \ 7.89(1\text{H}, \ dd, \ J=7.9, \ 1.7\text{Hz}), \ 7.26(1\text{H}, \ dd, \ J=7.9, \ 7.9\text{Hz}), \ 4.42(2\text{H}, \ q, \ J=7.3\text{Hz}), \ 4.18(2\text{H}, \ q, \ J=6.9\text{Hz}), \ 1.43(3\text{H}, \ t, \ J=6.9\text{Hz}), \ 1.42(3\text{H}, \ t, \ J=7.3\text{Hz})$

30 [Example 417b]

Synthesis of 2-ethyoxy-3-nitrobenzyl alcohol

[0101] To a mixture of the compound (117 mg) obtained in Example 417a, tetrahydrofuran (5 ml) and methanol (2 ml), lithium borohydride (10.7 mg) was added. The reaction mixture was stirred at room temperature for 15 h, and, after addition of water, concentrated under reduced pressure. To the resulting residue, 2 N HCl was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate=n-hexane = 1 : 2) to give the titled compound quantitatively.

¹H-NMR(CDCl₃) δ:7.77(1H, d, J=7.9Hz), 7.67(1H, d, J=7.3Hz), 7.22(1H, dd, J=7.9, 7.3Hz), 4.80(2H, s), 4.08(2H, q, J=6.8Hz), 2.10(1H, brs), 1.44(3H, t, J=6.8Hz)

[Example 417c]

Synthesis of 2-ethoxy-3-nitrobenzyl bromide

[0102] To a mixture of the compound (3.13 g) obtained in Example 417b, carbon tetrabromide (5.26 g) and methylene chloride (100 ml), triphenylphosphine (4.16 g) was added under ice cooling. The reaction mixture was stirred under ice cooling for 30 min and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate: n-hexane = 1:9) to give 3.59 g of the titled compound (yield, 87%).

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<sup>55</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>)
δ:7.78(1H, dd, J=7.9, 1.7Hz), 7.65(1H, dd, J=7.6, 1.7Hz), 7.20(1H, dd, J=7.9, 7.6Hz), 4.57(2H, s), 4.17(2H, q, J=6.9Hz), 1.49(3H, t, J=6.9Hz)
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[Example 417d]

Synthesis of N-(2-ethoxy-3-nitrophenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0103] A mixture of iminodicarboxylic acid di-t-butyl ester (3.23 g), dimethylformamide (50 ml) and sodium hydride (0.57 g) was stirred under ice cooling for 1 h and then a mixture of the compound (3.51 g) obtained in Example 417c and dimethylformamide (20 ml) was added under ice cooling. The reaction mixture was stirred at room temperature for 14 h and, after addition of 2 N HCl, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 9) to give 5.09 g of the titled compound (yield, 95%).

1H-NMR(CDCl₃)

 δ :7.72(1H, dd, J=7.9, 1.3Hz), 7.38(1H, dd, J=7.3, 1.3Hz), 7.17(1H, dd, J=7.9, 7.3Hz), 4.91(2H, s), 4.06(2H, q, J=6.9Hz), 1.45(18H, s), 1.44(3H, t, J=6.9Hz)

[Example 417e]

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Synthesis of N-(3-amino-2-ethoxyohenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0104] To a mixture of the compound (5.09 g) obtained in Example 417d, nickel (II) chloride hexahydrate (61 mg) and methanol (130 ml), sodium borohydride (1.46 g) was added. The reaction mixture was stirred at room temperature for 20 min and, after addition of 2 N HCl, adjusted to pH 8 with a saturated aqueous sodium hydrogencarbonate solution and then concentrated under reduced pressure. To the resulting residue, water was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 4) to give the titled compound (yield, 85%).

¹H-NMR(CDCl₃) 8:6.86(1H, dd, J=7.9, 7.6Hz), 6.63(1H, dd, J=7.6, 1.0Hz), 6.53(1H, dd, J=7.9, 1.0Hz), 4.85(2H, s), 3.90(2H, q, J=6.9Hz), 3.74(2H, brs), 1.43(18H, s), 1.41(3H, t, J=6.9Hz)

Example 500b

Synthesis of N-(5-amino-2-(pyrazole-1-yl)phenylmethyl)carbamic acid t-butyl ester

[Example 500a]

Synthesis of N-(5-nitro-2-(pyrazole-1-yl)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0105] To a mixture of pyrazole (1.0 g) and dimethylsulfoxide (50 ml), sodium hydride(0.54 g) was added under ice cooling. The reaction mixture was stirred under ice cooling for 1 h and then a solution of N-(2-fluoro-5-nitrophenylmethyl)iminodicarboxylic acid di-t-butyl ester (5.0 g) in dimethyl sulfoxide (50 ml) was added. The reaction mixture was stirred at room temperature for 15 h and, after addition of water, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1:4) to give the titled compound (yield, 73%).

 1 H-NMR(CDCl₃) δ :8.22-8.19(2H, m), 7.79-7.78(2H, m), 7.50(1H, d, J=9.6Hz), 6.53(1H, dd, J=2.3, 2.0Hz), 4.95(2H, s), 1.46(18H, s)

[Example 500b]

Synthesis of N-(5-amino-2-(pyrazole-1-yl)phenylmethyl)carbamic acid t-butyl ester

[0106] To a mixture of the compound (4.15 g) obtained in Example 500a, nickel (II) chloride hexahydrate (0.183 g) and methanol (300 ml), sodium borohydride (2.43 g) was added. The reaction mixture was stirred at room temperature for 55 min; thereafter, 2 N HCl was added to render the reaction solution acidic and then a saturated aqueous sodium

hydrogencarbonate solution was added to render the reaction solution basic; subsequently, the reaction mixture was concentrated under reduced pressure. To the resulting residue, water was added and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate/n-hexane to give the titled compound (yield, 89%).

¹H-NMR(CDCl₃) δ:7.69(1H, d, J=2.0Hz), 7.06(1H, d, J=8.3Hz), 6.86-6.83(1H, m), 6.60(1H, dd, J=8.3, 2.3Hz), 6.41(1H, dd, J=2.0, 1.3Hz), 5.62(1H, brs), 4.01(2H, d, J=6.6Hz), 3.82(2H, brs), 1.43(9H, s)

Example 519e

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Synthesis of 3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxyaniline

15 [Example 519a]

Synthesis of 5-bromo-4-chloro-2-fluoronitrobenzene

[0107] To a mixture of 4-chloro-2-fluoronitrobenzene (1.00 g), silver sulfate (1.95 g) and concentrated sulfuric acid (5 ml), bromine (0.32 ml) was added under ice cooling and the resulting mixture was stirred at 0°C for 30 min, then at room temperature for 1 h. The reaction mixture was put into ice water and subjected to extraction with ether. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution sequentially, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 1.38 g of the titled compound (yield, 95%).

¹H-NMR(CDCl₃) 8:7.47(1H, d, J=9.9Hz), 8.37(1H, d, J=7.3Hz)

[Example 519b]

Synthesis of 5-bromo-4-chloro-2-fluoro-3-(trifluoromethylcarbonylaminomethyl)nitrobenzene

[0108] A mixture of the compound (204 mg) obtained in Example 519a, N-hydroxymethyl-2,2,2-trifluoroacetamide (115 mg) and 10% fuming sulfuric acid (1.6 ml) was stirred at 80°C for 10 h. The reaction mixture was cooled, put into ice water and subjected to extraction with ether. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure.

[0109] The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1: 3) to give 85.1 mg of the titled compound (yield, 28%).

```
<sup>1</sup>H-NMR(CDCl<sub>3</sub>)
δ:4.86(2H, d, J=4.0Hz), 6.73(1H, brt), 8.39(1H, d, J=7.3Hz)
```

[Example 519c]

Synthesis of 5-bromo-3-(t-butoxycarbonylaminomethyl)-4-chloro-2-fluoronitrobenzene

[0110] A mixture of the compound (601 mg) obtained in Example 519b, concentrated sulfuric acid (3 ml) and methanol (12 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure and, after being rendered basic by addition of a 2 N aqueous sodium hydroxide solution, it was subjected to extraction with methylene chloride (20 ml). To the organic layer, di-t-butyl dicarbonate (414 mg) and a 2 N aqueous sodium hydroxide solution (10 ml) were added at room temperature and the resulting mixture was stirred at room temperature for 2 h. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, chloroform) to give 402 mg of the titled compound (yield, 66%).

```
<sup>1</sup>H-NMR(CDCl<sub>3</sub>)
δ:1.44(9H, s), 4.57-4.66(2H, m), 5.01(1H, brt), 8.31(1H, d, J=7.6Hz)
```

[Example 519d]

Synthesis of 5-bromo-3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxynitrobenzene

5 [0111] To a mixture of the compound (200 mg) obtained in Example 519c, ethanol (36 μl) and tetrahydrofuran (5 ml), sodium hydride (content, 60%; 25 mg) was added under ice cooling. The reaction mixture was stirred at 0°C for 2 h and then water and ether were added. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 4) to give 197 mg of the titled compound (yield, 92%).

```
^{1}H-NMR(CDCl<sub>3</sub>) δ:1.45(9H, s), 1.47(3H, t, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.62(2H, d, J=5.9Hz), 4.93(1H, brt), 8.10(1H, s)
```

15 [Example 519e]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxyaniline

[0112] Using the compound obtained in Example 519d as a starting material, the procedure of Example 3 was repeated to give the titled compound (86%).

```
^{1}H-NMR(DCDI<sub>3</sub>) δ:1.44(3H, t, J=7.3Hz), 1.45(9H, s), 3.78(2H, brs), 3.92(2H, q, J=7.3Hz), 4.47(2H, d, J=5.3Hz), 4.91(1H, brt), 6.63(1H, d, J=8.3Hz), 6.94(1H, d, J=8.3Hz)
```

Example 520d

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-6-mothylaniline

30 [Example 520a]

Synthesis of 3-methyl-6-nitro-2-(trifluoromethylcarbonylaminomethyl)phenol

[0113] Using 5-methyl-2-nitrophenol as a starting material, the procedure of Example 545b was repeated to give the 35 titled compound (16%).

```
<sup>1</sup>H-NMR(CDCl<sub>3</sub>)
δ:2.57(3H, s), 4.67(2H, d, J=6.3Hz), 6.89(1H, d, J=8.6Hz), 7.00(1H, brs), 8.00(1H, d, J=8.6Hz), 11.23(1H, s)
```

#0 [Example 520b]

Synthesis of 2-(t-butoxycarbonylaminomethyl)-4-methyl-6-nitrophenol

[0114] A mixture of the compound (100 mg) obtained in Example 520a, potassium carbonate (99.4 mg), water (1.0 ml) and methanol (6.0 ml) was stirred at room temperature for 3 h and then di-t-butyl dicarbonate (157 mg) was added. The reaction mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. To the resulting residue, a saturated aqueous sodium chloride solution was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 3 : 17) to give the titled compound (yield, 70%).

```
^{1}H-NMR(CDCl<sub>3</sub>) 8:1.43(9H,s),\ 2.55(3H,\ s),\ 4.44(2H,\ d,\ J=6.3Hz),\ 5.17(1H,\ brs),\ 6.82(1H,\ d,\ J=8.6Hz),\ 7.94(1H,\ d,\ J=8.6Hz),\ 11.11(1H,\ s)
```

[Example 520c]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-4-methylnitrobenzene

[0115] A mixture of the compound (350 mg) obtained in Example 520b, cesium carbonate (404 mg), dimethylformamide (15 ml) and ethyl iodide (0.4 ml) was stirred at 60°C for 2 h. To the reaction mixture, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 2 : 8) to give the titled compound quantitatively.

¹H-NMR(CDCl₃)

δ:1.44(9H, s), 1.48(3H, t, J=6.9Hz), 2.49(3H, s), 4.03(2H, q, J=6.9Hz), 4.41(2H, d, J=5.6Hz), 4.86(1H, brs), 7.03(1H, d, J=8.6Hz), 7.72(1H, d, J=8.6Hz)

15 [Example 520d]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-4-methylaniline

[0116] Using the compound obtained in Example 520c as a starting material, the procedure of Example 3 was 20 repeated to give the titled compound (92%).

¹H-NMR(CDCl₃)

δ:1.43(3H, t, J=6.9Hz), 1.44(9H, s), 2.26(3H, s), 3.61(2H, brs), 3.89(2H, q, J=6.9Hz), 4.34(2H, d, J=5.3Hz), 4.70(1H, brs), 6.61(1H, d, J=7.9Hz), 6.75(1H, d, J=7.9Hz)

Example 538e

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Synthesis of N-(3-amino-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

30 [Example 538a]

Synthesis of 3-nitro-2-(n-propoxy)benzoic acid n-propyl ester

[0117] Using 3-nitrosalicylic acid as a starting material and also using n-propyl iodide as a reagent, the procedure of Example 417a was repeated to give the titled compound (yield, 29%).

¹H-NMR(CDCl₃)

8:7.98(1H, dd, J=7.6, 1.7Hz), 7,87(1H, dd, J=7.9, 1.7Hz), 7.24(1H, dd, J=7.9, 7.6Hz), 4.31(2H, t, J=6.9Hz), 4.05(2H, t, J=6.9Hz), 1.90-1.71(4H, m), 1.08-0.97(6H, m)

[Example 538b]

Synthesis of 3-nitro-2-(n-propoxy)benzyl alcohol

45 [0118] Using the compound obtained in Example 538a as a starting material, the procedure of Example 417b was repeated to give the titled compound (yield, 70%).

¹H-NMR(CDCl₃)

δ:7.76(1H, dd, J=8.3, 1.3Hz), 7.68(1H, dd, J=7.3, 1.3Hz), 7.21(1H, dd, J=8.3, 7.3Hz), 4.80(2H, s), 3.96(2H, t, J=6.9Hz), 2.13(1H, brs), 1.91-1.77(2H, m), 1.04(3H, t, J=7.3Hz)

[Example 538c]

Synthesis of 3-nitro-2-(n-propoxy)benzyl bromide

[0119] Using the compound obtained in Example 538b as a starting material, the procedure of Example 417c was repeated to give the titled compound (yield, 95%).

1H-NMR(CDCl₃)

 δ :7.77(1H, dd, J=7.9, 1.3Hz), 7.64(1H, dd, J=7.9, 1.3Hz), 7.19(1H, dd, J=7.9, 7.9Hz), 4.57(2H s), 4.05(2H, t, t, t) J=6.6Hz), 1.96-1.83(2H, m), 1.07(3H, t, J=7.3Hz)

[Example 538d]

Synthesis of N-(3-nitro-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0120] Using the compound obtained in Example 538c as a starting material, the procedure of Example 417d was repeated to give the titled compound (yield, 62%).

1H-NMR(CDCl₃)

8:7.70(1H, dd, J=7.9, 1.3Hz), 7.37(1H, dd, J=7.9, 1.3Hz), 7.16(1H, dd, J=7.9, 7.9Hz), 4.91(2H, s), 3.94(2H, t, J=6.6Hz), 1.91-1.80(2H, m), 1.45(18H, s), 1.05(3H, t, J=7.3Hz)

[Example 538e]

Synthesis of N-(3-amino-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

20 [0121] Using the compound obtained in Example 538d as a starting material, the procedure of Example 417e was repeated to give the titled compound quantitatively.

1H-NMR(CDCI₃)

δ:6.86(1H, dd, J=7.9, 7.6Hz), 6.63(1H, d, J=7.9Hz), 6.52(1H, d, J=7.6Hz), 4.85(2H, s), 3.78(2H, t, J=6.6Hz), 3.74(2H, brs), 1.89-1.75(2H, m), 1.43(18H, s), 1.07(3H, t, J=7.3Hz)

Example 542a

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Synthesis of N-(3-amino-2-(i-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0122] Using 3-nitrosalicylic acid as a staring material and also using i-propyl iodide as a reagent, the procedures of Examples 417a-417e were repeated to give the titled compound.

¹H-NMR(CDCl₃)

δ.6.85(1H, dd, J=7.9, 7.6Hz), 6.62(1H, d, J=7.6Hz), 6.53(1H, d, J=7.9Hz), 4.83(2H, s), 4.26-4.15(1H, m), 3.69(2H, brs), 1.42 (18H, s), 1.31(6H, d, J=6.3Hz)

Test Examples

Test Example 1

[0123] Compounds of the invention were evaluated for their inhibitory effect on the presently known three NOS isoforms.

[0124] Crude enzymes of the respective NOS isoforms were prepared by the following procedures (Nagafuji et al., 45 Neuroreport 6, 1541 - 1545, 1995).

[0125] The crude enzyme of nNOS was prepared by the following procedure. Normal untreated male Sprague Dawley (SD) rats (body weight, 300 - 400 g) were decapitated; the whole brain was immediately taken out from each animal and the cerebral cortex was separated on ice. Then, 5 volumes of 50 mM Tris-HCl containing 1 mM DTT (pH 7.4) was added and the mixture was homogenized for 3 min and centrifuged at 1,000 x g for 10 min. The resulting supernatant 50 was further centrifuged at 100,000 x g for 60 min and a soluble cytosolic fraction of the finally obtained supernatant was

used as the crude enzyme of nNOS.

[0126] The crude enzyme of iNOS was prepared by the following procedure. Rats were administered LPS (10 mg/kg) intraperitoneally and, 6 h later, perfused in a transcardiac manner with physiological saline containing 10 U/ml of heparin; thereafter, lungs were taken out. Subsequently, 5 volumes of 50 mM Tris-HCl containing 1 mM DTT (pH 7.4) 55 was added and the mixture was homogenized for 3 min, followed by centrifugation of the homogenate at 1,000 x g for 10 min. The resulting supernatant was centrifuged at 100,000 x g for 60 min and a soluble cytosolic fraction of the finally

[0127] The crude enzyme of eNOS was prepared by the following procedure. Cow pulmonary arterial endothelium

obtained supernatant was used as the crude enzyme of iNOS.

cells (CPAE) were cultured in a MEM medium containing 20% FBS. Several days later, the cells were detached from the flask using a 0.25% trypsin solution containing 1 mM EDTA and, after addition of a suitable amount of FBS, centrifuged at 1,000 rpm for 10 min. A suitable amount of Ca- and Mg-free phosphate buffer (pH 7.4) was added to the precipitating cells and they were centrifuged at 1,000 rpm for 10 min. The same step was repeated to wash the cells which, upon addition of 50 mM Tris-HCl (pH 7.4) containing 1% Triton X-100 and 1 mM DTT, were left to stand in ice for 1 h. Subsequently, the mixture was homogenized for 3 min and kept in ice for 30 min with occasional stirring. Finally, the mixture was centrifuged at 100,000 x g for 60 min and the resulting supernatant was used as the crude enzyme of eNOS.

[0128] The method of measuring NOS activity was basically the same as already reported by the present inventors and consisted of determining quantitatively the conversion of a substrate L-[³H]arginine to a reaction product L-[³H] citrulline (Nagafuji et al., in Brain Edema IX (Ito et al, eds.) 60, pp. 285 - 288, 1994; Nagafuji et al., Neuroreport 6, 1541 - 1545, 1995)

[0129] The reaction solution consisted of 100 nM L-[3 H] arginine, a prepared crude NOS enzyme sample (10 - 30 μ g/ml protein), 1.25 mM CaCl₂, 1 mM EDTA, 10 μ g/ml calmodulin, 1 mM NADPH, 100 μ M tetrahydrobiopterine, 10 μ M FAD, 10 μ M FMN and 50 mM Tris-HCl (pH 7.4), to which one of the compounds of the invention or one of the control compounds was added.

[0130] The reaction was started by addition of L-[³H] arginine. After incubation at 37°C for 10 min, the reaction was terminated by addition of 2 ml of 50 mM Tris-HCl (pH 5.5) containing 1 mM EDTA and placing the mixture on ice. The reaction solution was passed through a cation-exchange resin column (Dowex AG50WX-8, Na⁺ form, 3.2 ml) to separate the reaction product L-[³H] citrulline from the unreacted residual substrate L-[³H] arginine. The eluate was combined with another eluate resulting from the passage of a given amount of distilled water through the column and put into a minivial for recovery of L-[³H] citrulline. Thereafter, a scintillation fluid was added and the contained radioactivity was measured with a liquid scintillation counter to determine the amount of L-[³H] citrulline.

[0131] The activity of nNOS or eNOS was determined by subtracting the activity detected in the absence of CaCl₂ and calmodulin from the activity detected in the presence of CaCl₂ and calmodulin. The activity of iNOS was detected in the absence of CaCl₂ and calmodulin. The protein concentration of each crude enzyme sample was determined with a micro-assay kit of Bio Rad Co. Each Experiment was conducted in a duplicate.

[0132] Table 81 lists the mean values of IC_{50} (the concentration necessary to inhibit 50% activity) of all test compounds against each NOS isoform. The table also lists the ratios of IC_{50} values to each other as an index of selectivity.

Table 81

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	Inhibitory Action and Selectivity of Test Compounds against Three NOS Isoforms							
35	Example No. or Control Compound	Inhibitory action			Selectivity			
		nNOS	IC ₅₀ (nM) iNOS	eNOS	iNOS/nNOS	eNOS/nNOS	eNOS/iNOS	
	18	22.6	916.7	322.4	41	14	0.14	
40	52	79.8	N.D.	1476.7	-	19		
	53	86.1	N.D.	6624.3	•	77		
	57	70.8	N.D.	947.4	-	13	•	
45	61	126.0	N.D.	1614.9	•	13		
	151	126.2	N.D.	679.3	•	5	•	
	153	29.8	N.D.	586.1	•	20	•	
	458	20.8	N.D.	403.1		19	-	
50	460	111.7	N.D.	1244.3		11	<u>-</u>	
	462	16.4	N.D.	257.2	-	16	•	
	465	31.2	N.D.	1000.0	•	32	-	
55	466	35.5	N.D.	421.0	•	12	•	
	467	19.6	N.D.	274.6	-	14	-	
	468	56.3	N.D.	2481.0	-	44	•	

Table 81 (continued)

	Inhibitory Action and Selectivity of Test Compounds against Three NOS Isoforms						
5	Example No. or Control Inhibitory action S Compound		Selectivity	electivity			
		nNOS	IC ₅₀ (nM) iNOS	eNOS	iNOS/nNOS	eNOS/nNOS	eNOS/iNOS
	469	40.0	N.D.	994.0	•	25	-
	478	61.6	N.D.	447.5	•	7	•
10	479	66.9	N.D.	802.0	•	12	•
	481	78.1	N.D.	1984.5	-	25	-
	482	50.5	N.D.	1348.6	•	27	•
15	483	65.4	N.D.	711.0	-	11	•
	484	69.2	N.D.	1264.2	•	18	•
	485	54.4	1774.9	2882.4	32	53	1.6
	488	39.9	N.D.	297.9	•	8	-
20	489	22.1	N.D.	N.D.	•	-	-
	490	18.1	N.D.	347.5	•	19	•
	491	45.8	N.D.	1768.0	•	39	•
25	506	29.1	N.D.	1292.7	•	45	
	521	19.5	N.D.	485.2		25	•
	522	19.7	N.D.	398.4	•	20	-
	541	25.9	N.D.	712.6	•	28	•
30	543	12.5	N.D.	249.8		20	•
	L-NA	16.9	3464.3	68.2	205.0	4.0	0.02
	Notes: Symbol "N.D." means "not determined", and "-" means "uncalculable"						

INDUSTRIAL APPLICABILITY

[0133] The compounds of the present invention exhibit an outstanding nNOS or iNOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

45 Claims

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A compound represented by the general formula (I), or a possible tautomer, stereoisomer or optically active form
of the compound or a pharmaceutically acceptable salt thereof:

(where R₁ and R₂ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxycarbonyl group, or R₁ and R₂ may combine together to form a 3- to 8-membered ring;

Fig. 15 R₃ and R₄ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R₃ and R₄ may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms; R₅ is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;

 X_1 , X_2 , X_3 , and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl, group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkylthio group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=O)X_7$; where X_5 and X_6 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring;

 X_7 is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX_8X_9 ;

where X_8 and X_9 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_8 and X_9 may combine together to form a 3- to 8-membered ring;

A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;

n and m are each an integer of 0 or 1).

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2. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

 X_1 , X_2 , X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkyl group, X_5X_6 or X_5X_6 or X_5X_6 or X_5X_6 and

A is an optionally substituted benzene or pyridine ring.

- 3. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
- A is a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom (exclusive of an optionally substituted pyridine ring).
- 4. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optionally active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁ is a hydrogen atom;

 R_2 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group; and A is an optionally substituted benzene ring.

5. The compound of the general formula (1) according to claim 2 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

A is an optionally substituted pyridine ring.

50 6. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁ and R₂ are each a hydrogen atom;

R₅ is a hydrogen atom;

 X_1 , X_2 , X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group or NX_5X_6 ; and A is an optionally substituted benzene ring, an optionally substituted pyridine ring, an optionally substituted

pyrimidine ring, an optionally substituted oxazole ring, or an optionally substituted thiazole ring.

7. The compound of the general formula (1) according to claim 6 or a possible tautomer, stereoisomer or optionally active form of the compound or a pharmaceutically acceptable salt thereof, in which:

A is an optionally substituted benzene ring or an optionally substituted pyridine ring.

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8. The compound of the general formula (1) according to any one of claims 1 - 7 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

 R_3 and R_4 which may be the same or different are each a hydrogen atom or a lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic ring having 3 - 10 carbon atoms.

- 9. The compound of the general formula (1) according to any one of claims 1 8 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
- X_1, X_2, X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group optionally substituted by a phenyl group or NX_5X_6 ; where X_5 and X_6 which may be the same or different are each a hydrogen atom, a lower alkyl group optionally substituted by a phenyl group or an acyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring.
 - 10. The compound of the general formula (1) according to claim 6, 8 or 9 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which A is an optionally substituted benzene ring or an optionally substituted pyridine ring, with the optional substituent being a nitro group, a lower alkyl group or a lower alkylthio group.
 - 11. The compound of the general formula (1) according to any one of claims 1 8 or claim 10 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
- X_1, X_2, X_3 , or X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group or NX_5X_6 ; where X_5 and X_6 which may be the same or different are each a hydrogen atom, a lower alkyl group or an acyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring.
- 12. The compound of the general formula (1) according to any one of claims 1 11 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

m and n are each 0; and the substituents other than X_1 , X_2 , X_3 , and X_4 are meta-substituted on the benzene ring.

40 13. The compound of the general formula (1) according to any one of claims 1 - 11 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

m + n = 1; and the substituents other than X_1 , X_2 , X_3 and X_4 are ortho- or para-substituted on the benzene ring.

- 14. The compound of the general formula (1) according to claim 1 or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:
 - 2-(3-aminomethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-ethyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methoxy-3-nitropyridine,

 $\hbox{2-(3-aminomethyl-2-methylphenylamino)-6-methoxy-3-nitropyridine,}\\$

2-(4-aminoethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-fluorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-methylpyridine, 2-(3-(1-amino-1-methylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-methylpyridine, 2-(3-(1-amino-1-methylpyri

methylethyl)-phenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethoxyphenylamino)-4-methylpyridine.

- 2-(2-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-chlorophenylamino)-4-methylpyridine, 2-(3-(1-amino-cyclobutyl)phenylamino)-4-methylpyridine, 2-(4-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chlorophenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chloro-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-4-methylpyridine, and 2-(3-aminomethyl-2-(i-propoxy)phenylamino)-4-methylpyridine.
- 15. A nNOS inhibitor containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.

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16. A therapeutic of cerebrovascular diseases containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.

- 17. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral hemorrhage.
- 18. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is subarachnoid hemorrhage.
- 19. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral infarction.
- 30 20. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is atherothrombotic infarction.
 - 21. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is lacunar infarction.
 - 22. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is cardiogenic embolism.
 - 23. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is transient ischemic attack.
 - 24. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral edema.
- 40 25. A therapeutic of traumatic brain injury containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.
 - 26. A therapeutic of spinal injury containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
- 50 R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.
 - 27. An analgesic containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.

28. The therapeutic according to claim 27, wherein the type of pain is headache.

- 29. The therapeutic according to claim 28, wherein the subtype of headache is migraine.
- 30. The therapeutic according to claim 28, wherein the subtype of headache is tension headache.
- The therapeutic according to claim 28, wherein the subtype of headache is cluster headache or chronic paroxysmal headache.
- 32. A therapeutic of Parkinson's disease containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.
- 33. A therapeutic of Alzheimer's disease containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , X_3 , X_4 , n, m and A have the same meanings as defined in claim 1.
- 34. A therapeutic of seizure containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , X_3 , X_4 , n, m and A have the same meanings as defined in claim 1.
 - 35. A therapeutic effective against morphine tolerance or dependence containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
- 30 R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.

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- 36. A therapeutic of septic shock containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.
- 37. A therapeutic of chronic rheumatoid arthritis containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof. in which:
 - R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , X_3 , X_4 , n, m and A have the same meanings as defined in claim 1.
- 38. A therapeutic of osteoarthritis containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.
- 39. A therapeutic of viral or nonviral infections containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:
 - R_1 , R_2 , R_3 , R_4 , R_5 , X_1 , X_2 , X_3 , X_4 , n, m and A have the same meanings as defined in claim 1.
 - 40. A therapeutic of diabetes mellitus containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R₁, R₂, R₃, R₄, R₅, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1.

A process for producing a compound according to claim 1 by the reaction pathway (A):
 Reaction pathway (A)

provided that in the general formula (1), (2) or (3),

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 R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_3 , X_4 , n, m and A have the same meanings as defined in claim 1; R_3 is a hydrogen atom or an optionally substituted lower alkyl group; and L is a leaving group.

20 42. A process for producing a compound according to claim 1 by the reaction pathway (B): Reaction pathway (B)

provided that in the general formula (1), (9) or (10),

R₁, R₂, R₃, R₄, X₁, X₂, X₃, X₄, n, m and A have the same meanings as defined in claim 1; R₅ is a hydrogen atom or an optionally substituted lower alkyl group; and L is a leaving group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁶ C07C211/54, C07C211/56, C07C209/10, C07D239/42, C07D241/20, C07D263/48, C07D207/335, C07D207/337, C07D401/12, C07D205/04,					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Int.	Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁵ C07C1/00-409/44, C07D201/00-521/00, A61K6/00-49/04				
	Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
	ata base consulted during the international search (nam ONLINE	ne of data hase and, where practicable, s	earch terms used)		
C. DOCU	MENTS CONSIDERED TO BE RELEVANT				
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X Furthe	er documents are listed in the continuation of Box C.	See patent family annex.			
Special	Special categories of cited documents: T later document published after the international filling date or priority.				
conside "E" carlier "L" docum	considered to be of particular relevance "E" cartier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or which is "X" document of particular relevance; the claimed invention cannot be considered to involve an inventive step				
special					
"P" docum	ent published prior to the international filing date but later than ority date claimed	being obvious to a person skilled in the "&" document member of the same patent for	nc		
Date of the Marc	actual completion of the international search: h 30, 1998 (30. 03. 98)	Date of mailing of the international sea April 21, 1998 (21			
Name and r Japa	nailing address of the ISN anese Patent Office	Authorized officer			
Facsimile N	io	Telephone No.			

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

		PC175	P31/04102
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x	JP, 5-186431, A (Elf Sanofi), July 27, 1993 (27. 07. 93)		1, 40
A	& EP, 519831, A1 & FR, 2677984, A1 & US, 5274104, A		2-39, 41, 42
x	WO, 96/36620, Al (SMITHKLINE BEECHAM SPA November 21, 1996 (21. 11. 96)	Δ),	1
A	& EP, 825991, A1		2-42
х	JP, 8-505646, A (Abott Laboratories), June 18, 1996 (18. 06. 96)		1
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x	US, 4892578, A (FMC CORP.), January 9, 1990 (09. 01. 90) (Family: no	ne)	1
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	& DE, 32040/4, RI & 05, 443940/, R	
х	JP, 56-18969, A (Toyama Chemical Co., Ltd.),	1
.	February 23, 1981 (23. 02. 81)	2-42
A	& DE, 3027106, A1 & GB, 2056976, A & FR, 2461705, A1 & CA, 1131640, A1	2-42
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x	March 9, 1971 (09. 03. 71)	•
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х	MATHEW, A.E. et al., "Amino-substituted p-benzoquinones", J. Med. Chem., (1986) 29(9)	1
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International application No.
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Category*	Relevant to claim to			
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х	LEHMANN, Jochen et al., "Reductive cleavage of quinazoline-2,4-diones", Arch. Pharm. (Weinheim,		1	
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x	IRWIN, W.J. "Reduction of fused benzo[d]-and	arkin	1	
A	pyrido[3,2-d] pyridinones", J. Chem. Soc., Perkin Trans. 1(1972) (3) p.353-355		2-42	
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Î.	STERLING, J.D. et al., "Derivatives of 4-anilino- 3-nitrobenzenesulfonamide", US, 2834794, A (13 May 1958)		2-42	
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INTERNATIONAL SEARCH REPORT

International application No.
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A. (Continuation) CLASSIFICATION OF SUBJECT MATTER
C07D203/12, C07D401/12, C07D277/42, C07D295/12, C07D233/88, C07D213/74, C07D213/79, C07D213/81, C07D213/85, A61K31/135, A61K31/42, A61K31/505,
A61K31/40, A61K31/44, A61K31/395, A61K31/425, A61K31/445, A61K31/415, A61K31/44
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